Sayed A. Ahmed et al. / Journal of Pharmacy Research 2014,8(8),1185-1190

Research Article
ISSN: 0974-6943

Available online through
http://jprsolutions.info

Synthesis and Antimicrobial Activity of New Hydrazonothizole and Diazo-[1,3,4]thiadiazole Derivatives

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Received on:22-06-2014; Revised on: 17-07-2014; Accepted on:06-08-2014

ABSTRACT

Thiazoles and thiadiazole derivatives were synthesized from the reaction of hydrazonothiosemicarbazide derivatives and hydrazocarbodithioate with hydrazonoylhalides respectively. The new compounds were confirmed on the basis of elemental analysis and spectroscopic data and were screened antimicrobial activity.

KEYWORDS: Thiazoles, 1, 3, 4-thiadiazoles and antimicrobial activity.

INTRODUCTION:

Thiazoles are common substructures of monocyclic natural products that exhibit a rang of biological activities [1-7] including potent immunosuppressision inhibition of bacterial protein synthesis. Also, 1,3,4-thiadiazoles have activities on many biological systems such as antitumor,[8] hypoglycemic properties,[9] and antibacterial[10]. As an extension of our study and as apart of our program directed to the synthesis of different of thiazoles and thiadiazole derivatives for medicine. We report here the reactivity of hydrazonothiosemicarbazides toward hydrazonoyl halide derivatives.

RESULTS AND DISCUSSION

Treatment of aryl diazonium chlorides **1** with sodium salt of formylketone **2** afforded the hydrazonoformylketone derivatives **3**, which subjected to react with thiosemicarbaside to give the hydrazonothiosemicarbazide **5** not mercaptotriazole **4** or 2-mercaptopyrimidine **6**. The structure of compounds **5** were confirmed on the basis of elemental analysis and spectroscopic data. Thus, the IR spectrum of compound **5b** showed the absorption band that fix the presence of carbonyl group, so the compound **6** should be excluded. The ^{1}H NMR spectrum of **5b** revealed a singlet broad band at δ = 6.50 assignable to NH_2 group which is compatible with compound **5** not the mercaptotriazole **4**. Also the ^{13}C NMR of compound **5b** showed in downfield region the presence of band at δ = 190.22 assignable to CO group. Moreover, the mass spectrum of compound **5**b showed the molecular ion peak at m/z = 339 coincident with the molecular weight of the compound **5b** and its molecular formula$C_{17}H_{17}N_5OS$.

Confirmation of compounds **5** also, was given via their reaction with hydrazonoyl halides **7** to afford the diazothiazole derivatives **9** not the triazole derivatives **8** as in scheme 1. The proposed mechanism of the reaction was given as following. Firstly via acylation of the hydrazonothiosemicarbazide **5** by elimination of hydrochloric acid and then cyclized by loses of water molecule to afford thiazole derivatives **9**. Secondly via acylation of hydrazonothiosemicarbazide **5** through elimination of dehydrochlorination and then cyclized by loses of H_2S molecule to give the triazole derivatives **8**. According to the elemental analysis the produced compound contains sulfur atom that fix the first suggestion and the spectroscopic data confirmed the structures of compound **9**. Thus, the IR spectrum of compound **9c** showed only one absorption band of carbonyl group not two signals of two carbonyl groups. The ^{1}H NMR of compound **9c** revealed singlet band at δ = 2.02 assignable to CH_3 group and not at δ = 2.58 which is assignable to $COCH_3$. ^{13}C NMR spectrum of compound **9c** showed at downfield region only one signals at δ = 192.22 assignable to one carbonyl group not two signals of two carbonyl carbons and in upfield region showed band at δ = 17.22 assignable to CH_3 group not at 24.50 which is assignable to $COCH_3$. Moreover, the mass spectrum of compound **9c** revealed the molecular ion peak m/z = 502 coincident with the molecular formula $C_{25}H_{20}N_7OSCl$ so, all data fix the first suggestion. Further confirmation of compounds **9** were given via alternative chemical synthesis through the reaction of hydrazonothiosemicarbazide derivatives **5** with α-halo compounds

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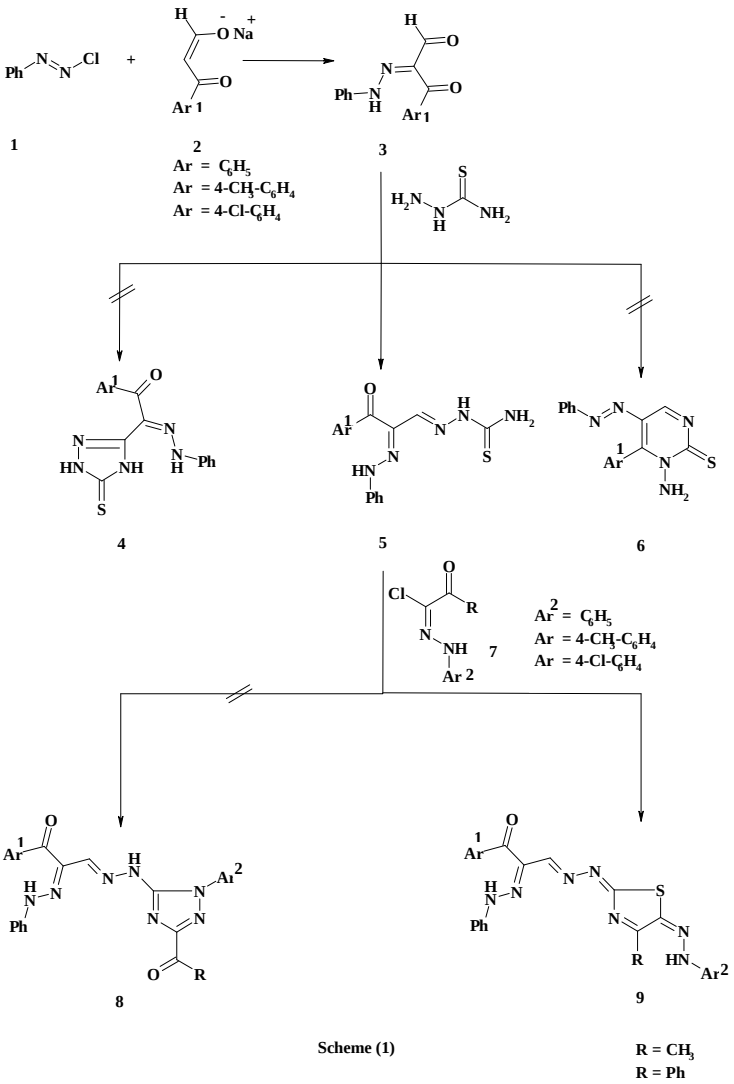
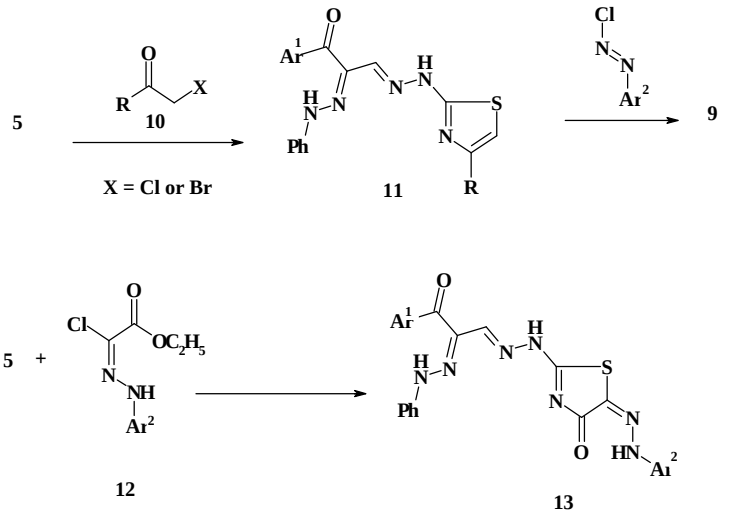
10 to give the corresponding thiazole derivatives **11**, which were subjected to coupled with diazonium chlorides **1** to furnished the diazothiazole derivatives **9**. The structures of compound **11** were confirmed on the basis of elemental analysis and spectroscopic evidences. Thus, the ^{1}H NMR of compound **11a** revealed singlet band at δ = 2.25 assignable to CH_3 and 6.99-8.51 assignable to aromatic H. Also, the mass spectrum of compound **11a** revealed the molecular ion peak m/z = 363 which is compatible with the molecular weight = 363.44 and molecular formula $C_{19}H_{17}N_5OS$. Further confirmations of compound **11** were given by coupling with diazonium chlorides to furnish the thiazoles **9**. Similar treatment of hydrazonothiosemicarbazide derivatives with hydrazonoyl halides **12** afforded the hydrazonothiazoles-3-one derivatives **13** as outlined in (scheme 2). The structures of compound **13** were confirmed on the basis of elemental analysis and spectroscopic data. Thus, IR spectrum of compound **13a** showed absorption band at 1730 and 1710 cm^{-1} of two different carbonyl groups. The ^{1}H NMR spectrum of compound **13a** showed free from quartet and triplet of OCH_2CH_3. Also, the mass spectrum of compound **13a** showed molecular ion peak at m/z = 469 which is compatible with the molecular formula $C_{24}H_{19}N_7O_2S$.

The synthetic potential of hydrazonoformylketone **3** was domenstrated via their reaction with carbodithioate **14** to furnish the diazocarbodithioate **15**. The structure of compounds **15** was elucidated according to elemental analysis and spectroscopic data. Treatment of carbodithioate **15** with hydrazonoyl chloride or nitrimine **7** or **12** in ethanolic triethylamine solution gave one isolable product according to tlc, and upon elemental analysis, spectroscopic data, the structure of the product was formulated as 1,3,4-thiadiazole derivatives **19** not the triazole derivatives **18**.

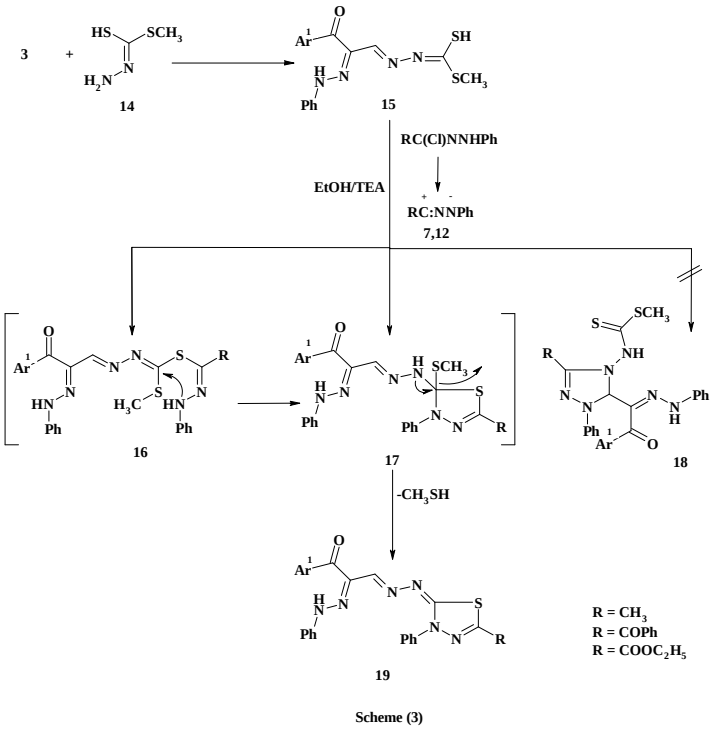
In view of the forgoing results, the mechanism of the reaction outlined in scheme 3 seems to be the most plausible pathway for the formation of structures **19**. The reaction involves initial formation of thiohydrazonate **15** which undergoes intermolecular cyclization as soon as it is formed to yield the intermediate **17** or via 1, 3-dipolar cycloaddition of nitrilimine which was prepared in situ from **7** or **12** with triethylamine. The latter was converted into the final product **19** via elimination of the methyl mercaptan. The structure of compounds **19** was confirmed on the basis of elemental analysis and spectroscopic data. Thus, the IR spectrum of compound **19a** showed the absorption band assignable to the carbonyl group. The ^{1}H NMR spectrum of compound **19a** showed bands free from the SCH_3 group. Further confirmation of compounds **19**a was given by the mass spectrum which showed the molecular ion peak at m/z = 468 coincident with the molecular weight 468.54 of the compound **19a** and with its molecular formula $C_{25}H_{20}N_6O_2S$. The ^{13}C NMR revealed bands free from SCH_3 at δ = 18 in upfield region.



Scheme (1)



Scheme (2)



Scheme (3)

Antimicrobial activity

The biological activity of these compounds against gram positive and gram negative bacteria as well as fungi was determined by filter paper and hole plate method [11-13], using amplicillin and tetracycline as controls and is shown in table (1).In general all tested compounds were capable of inhibiting the growth of gram positive and gram negative. Additionally compunds **9e-i, 19f,** and **19i** showed mortality rate activities against *Artemia salina* of 8, 10, 33, 32, 43, 70 and 11 %, respectively at concentrations of 10 μg /ml.

Table 1: Response of various microorganisms to some synthesized compounds *in vitro* (culture)

Microorganism Comp. No.	*Staphylococcus albus (G+)*	*Streptococcus faecalis (G+)*	*B. subtilis*	*E. coli*	*Aspergills Flvus (Fungus)*	*C. albiacns (Fungus)*
Amplicillin/ Tetracycline	**34R/27**	**37/31**	**33/30**	**39/34**	**0.0/0.0**	**20/37**
5a	17	12	5	3	0.0	18
5b	20	15	3	2	0.0	20
5c	24	13	10	8	0.0	17
9a	18	15	14	7	0.0	11
9b	15	19	13	11	0.0	10
9c	23	16	10	9	0.0	13
9f	20	17	19	10	0.0	16
9i	22	12	18	14	0.0	18
13a	15	10	16	11	0.0	12
13b	16	11	18	15	0.0	11
13c	20	15	20	12	0.0	14
19a	21	17	10	9	0.0	19
19c	22	19	20	2	0.0	20
19d	18	17	19	7	0.0	24
19f	22	20	22	11	0.0	23
19g	20	11	23	10	0.0	25
19i	21	13	20	12	0.0	24

R: Repellent action (not complete inhibition).
Values show zone of inhibition in mm. Diameter of the inhibition zones were: high (11–15 mm),moderate (6–10 mm), slight (1–5 mm), negative (0).

Experimental

All melting points were determined on a Gallenkamp electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer, and chemical shifts are expressed in *d* units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu and Elemental analyses were carried out at the Microanalytical Center of the Cairo University, Giza, Egypt and Microanalytical center of the Molecular and Bimolecular Chemistry at Gottingin University, Germany. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. Flash column chromatography was performed with silica (70-230 mesh).

Synthesis of 3-oxo-3-aryl-2-(phenyl-hydrazono)-propanaldehyde 3a-c: A solution of (0.01 mol) sodium salt of 1-aryl-3-hydroxy-2-propene-1-one **2** (0.01 mol) and benzenediazonium chloride **1** (0.01 mol) was stirred at 5^{0}C for 1h. The precipitated product was acidified by acetic acid and the solid product was filtered off and recrystallized from ethanol. The product was prepared as orange powdered and in excellent yields (90 %). **3a:** Orange, (EtOH), yield (70 %), mp 75-78°, ir (KBr): ν (cm^{-1}): 3450 (NH), 3100 (aromatic CH), 1722 (CO), 1620 (C=N) and 1615(C=C). *Anal*. Calcd. for $C_{15}H_{12}N_2O_2$ (252): C, 71.42; H, 4.79; N, 11.10; O, 12.68. Found: C, 71.46; H, 4.81; N, 11.13; O, 12.65. **3b**: Orange, (EtOH), yield (85 %), mp 85-88°, ir (KBr): ν (cm^{-1}): 3460 (NH), 3090 (aromatic CH), 1720 (CO), 1622 (C=N) and 1610(C=C); ^{1}H nmr (300 MHz, DMSO) δ_H (ppm): 2.49 (s, 3H, CH_3) 7.65-8.79 (m, 9H, ArH), 9.8 (s, 1H, NH) and 13.5 (s, 1H, CHO); ms: (m/z) (M^+ = 252 (30 %). *Anal*. Calcd. for $C_{16}H_{14}N_2O_2$ (266): C, 72.17; H, 5.30; N, 10.52; O, 12.02. Found: C, 72.20; H, 5.33; N, 10.54; O, 12.05. **3c**: Yellow, (EtOH), yield (69 %), mp 115-118°. *Anal*. Calcd. for $C_{15}H_{11}N_2O_2Cl$ (286): C, 62.84; H, 3.87; N, 9.77; O, 11.16. Found: C, 62.86; H, 3.90; N, 9.79; O, 11.12.

Synthesis of 3-oxo-3-aryl-2-(phenyl-hydrazono)-propylidene]-thiosemicarbazide derivatives 5a-c:

To a solution of diazoformylketone **3** (0.01 mol) in ethanol, thiosemicarbazide (0.01 mol) was added over a period of 15 min and then the reaction mixture was stirred at room temperature for 3 h. The residual solid product was collected as a yellow powdered in very good yields and purified by recrystallization from the proper solvent. **5a**: Yellow, (dioxan), yield (72.5 %), mp 210-213°, ir (KBr): ν (cm^{-1}): 3450, 3250, 3200, 3050 (NH, NH_2), 3080 (aromatic CH), 1720 (CO), 1625 (C=N) and 1610(C=C). *Anal*. Calcd. for $C_{16}H_{15}N_5OS$ (325): C, 59.06; H, 4.65; N, 21.52; O, 4.92; S, 9.85. Found: C, 59.04; H, 4.62; N, 21.56; O, 4.95; S, 9.82. **5b:** Colorless, (EtOH), yield (75 %), mp 230-233°, ir (KBr): ν (cm^{-1}): 3434, 3250, 3150, 3050 (NH, NH_2), 3080 (aromatic CH), 1715 (CO), 1620 (C=N) and 1601(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 2.49 (s, 3H, CH_3), 3.76 (s, 1H, SH, tautomeric) 6.5(s, br, 2H, NH_2), 7.32-8.53 (m, 10H, ArH), 9.50 (s, br, 1H, NH) and 11.80 (s, br, 1H, NH); ^{13}C

nmr δ (ppm): d = 190.22 (C=O), 182.55 (C=S) 169.22 (C=N), 145.45 (CH=)137.50.2-126.56 (aromatic carbons) and in upfield region: 17.22 (CH_3); ms: (m/z) (M^+ = 339 (15 %), 321, (23 %), 185 (26%), 119 (75 %) 91 (76 %) and 65 (80 %). *Anal* . Calcd. for $C_{17}H_{17}N_5OS$ (339): C, 60.16; H, 5.05; N, 20.63; O, 4.71; S, 9.45. Found: C, 60.12; H, 5.08; N, 20.66; O, 4.75; S, 9.42. **5c:** Colorless, (EtOH), yield (70 %), mp 240-243°, ir (KBr): ν (cm^{-1}): 3504, 3350, 3230, 3070 (NH, NH_2), 3060 (aromatic CH), 1718 (CO), 1615 (C=N) and 1610(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 3.66 (s, 1H, SH, tautomeric), 6.9(s, br, 2H, NH_2), 7.51-8.22 (m, 10H, ArH), 9.91 (s, br, 1H, NH) and 11.85 (s, br, 1H, NH); ms: (m/z) (M^+ = 360 (10 %), 185 (22%), 119 (75 %) 91 (70 %) and 65 (82 %). *Anal* . Calcd. for $C_{16}H_{14}N_5OSCl$ (359.5): C, 53.41; H, 3.92; N, 19.46; O, 4.45; S, 8.91. Found: C, 53.47; H, 3.95; N, 19.42; O, 4.48; S, 8.94.

Synthesis of 3-{[4-substituted-5-aryl-hydrazono)-5H-thiazol-2-ylidene]-hydra-zono}-1-aryl-2-(phenyl-hydrazono)-propan-1-one derivatives 9a-r and 13a-i:

Method A: An equimolar amount of thioamides **5** (0.01 mol) and hydrazonoyl halides **7 a,b** or **12** were stirred in ethanol containing triethylamine (0.005 mol) at room temperature for 3 h. The resulting solid products were collected and crystallized from the proper solvent to give orange powdered in very good yields.

Method B: A solution of 1,3-thiazole **11** and benzendiazonium chloride **1** was stirred in ethanol-sodium acetate mixture at room temperature for 3h. The solid product was collected after acidified by hydrochloric acid and crystallized from the proper solvent to give compounds **9**.

9a: Colorless, (dioxan), yield (80 %), mp 235-238°, ir (KBr): ν (cm^{-1}): 3250, 3170, (NH,), 3090 (aromatic CH), 1722 (CO), 1617 (C=N) and 1600 (C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 2.00 (s, 3H, CH_3), 7.35-8.00 (m, 16H, ArH), 11.50 (s, br, 1H, NH) and 13.50 (s, br, 1H, NH); ^{13}C nmr δ (ppm): d = 185.22 (C=O), 162.02 (C-2) 158.22 (C-4), 150.45 (CH=), 140.55(C-5), 135.50.2-126.56 (aromatic carbons) and 15.27 (CH_3); ms: (m/z) (M^+ = 467 (10 %), 160 (28%), 118 (70 %), 77 (77 %) and 65 (65 %). *Anal* . Calcd. for $C_{25}H_{21}N_7OS$ (467): C, 64.22; H, 4.53; N, 20.97; O, 3.42; S, 6.86. Found: C, 64.25; H, 4.56; N, 20.95; O, 3.40; S, 6.84. **9b:** Yellow, (dioxan), yield (75 %), mp 270-273°; ir (KBr): ν (cm^{-1}): 3400, 3200, 3090 (NH,), 3130 (aromatic CH), 1720 (CO), 1625 (C=N) and 1615(C=C). *Anal* . Calcd. for $C_{26}H_{23}N_7OS$ (481): C, 64.85; H, 4.81; N, 20.36; O, 3.32; S, 6.66. Found: C, 64.83; H, 4.84; N, 20.31; O, 3.35; S, 6.64. **9c:** Yellow, (dioxan), yield (73 %), mp 230-232°, ir (KBr): ν (cm^{-1}): 3350, 3150, 3050 (NH,), 3110 (aromatic CH), 1725 (CO), 1621 (C=N) and 1612(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 2.02 (s, 3H, CH_3), 7.32-8.01 (m, 15H, ArH), 11.50 (s, br, 1H, NH) and 13.80 (s, br, 1H, NH); ^{13}C nmr δ (ppm): d = 192.22 (C=O), 160.55 (C-2) 169.22 (C-4), 145.45 (CH=), 142.55(C-5), 137.50.2-126.56 (aromatic carbons) and 17.22 (CH_3); ms: (m/z) (M^+ = 502 (10 %), 218, (23 %), 160 (20%), 118 (75 %), 77 (75 %) and 65 (60 %). *Anal* . Calcd. for $C_{25}H_{20}N_7OSCl$ (502): C, 59.82; H, 4.02; N, 19.53; O, 3.19; S, 6.39. Found: C, 59.84; H, 4.05; N, 19.51; O, 3.21; S, 6.36. **9d:** Yellow, (EtOH), yield (71 %), mp 265-267°, ir (KBr): ν (cm^{-1}): 3450, 3250, 3090 (NH,), 3120 (aromatic CH), 1720 (CO), 1622 (C=N) and 1615(C=C). *Anal* . Calcd. for $C_{26}H_{23}N_7OS$ (481): C, 64.85; H, 4.81; N, 20.36; O, 3.32; S, 6.66. Found: C, 64.88; H, 4.84; N, 20.32; O, 3.31; S, 6.64. **9e:** Colorless, (EtOH), yield (77 %), mp 244-246°, ir (KBr): ν (cm^{-1}): 3400, 3240, 3050 (NH,), 3100 (aromatic CH), 1722 (CO), 1622 (C=N) and 1610(C=C). *Anal* . Calcd. for $C_{27}H_{25}N_7OS$ (495): C, 65.43; H, 5.08; N, 19.78; O, 3.23; S, 6.47. Found: C, 65.46; H, 5.05; N, 19.79; O, 3.20; S, 6.43. **9f:** Colorless, (dioxan), yield (69 %), mp 255-256°. *Anal* . Calcd. for $C_{26}H_{22}N_7OSCl$ (516): C, 60.52; H, 4.30; N, 19.00; O, 3.10; S, 6.21. Found: C, 60.56; H, 4.33; N, 19.02; O, 3.13; S, 6.19. **9g:** Colorless, (EtOH), yield (75 %), mp 238-241°. *Anal* . Calcd. for $C_{25}H_{20}N_7OSCl$ (502): C, 59.82; H, 4.02; N, 19.53; O, 3.19; S, 6.39. Found: C, 59.85; H, 4.05; N, 19.55; O, 3.22; S, 6.35. **9h:** Yellow, (MeOH), yield (78 %), mp 250-253°. *Anal* . Calcd. for $C_{26}H_{22}N_7OSCl$ (516): C, 60.52; H, 4.30; N, 19.00; O, 3.10; S, 6.21. Found: C, 60.56; H, 4.34; N, 19.03; O, 3.13; S, 6.18. **9i:** Yellow, (EtOH), yield (70 %), mp 260-263°, ir (KBr): ν (cm^{-1}): 3360, 3250, 3050 (NH,), 3080 (aromatic CH), 1720 (CO), 1618 (C=N) and 1611(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 1.85 (s, 3H, CH_3), 7.55-8.52 (m, 14H, ArH), 11.10 (s, br, 1H, NH) and 12.80 (s, br, 1H, NH). ^{13}C nmr δ (ppm): d = 190.22 (C=O), 160.11 (C-2) 167.20 (C-4), 140.45 (CH=), 139.55(C-5), 136.50.2-125.56 (aromatic carbons) and 16.20 (CH_3); ms: (m/z) (M^+ = 536 (10 %). *Anal* . Calcd. for $C_{25}H_{19}N_7OSCl_2$ (536): C, 55.98; H, 3.57; N, 18.28; O, 2.98; S, 5.98. Found: C, 56.02; H, 3.59; N, 18.25; O, 2.95; S, 5.95. **9j:** Yellow, (EtOH), yield (66 %), mp 244-245°. *Anal* . Calcd. for $C_{30}H_{23}N_7OS$ (529): C, 68.04; H, 4.38; N, 18.51; O, 3.02; S, 6.05. Found: C, 68.01; H, 4.35; N, 18.53; O, 3.04; S, 6.02. **9k:** Colorless, (EtOH), yield (63 %), mp 236-238°. *Anal* . Calcd. for $C_{31}H_{25}N_7OS$ (543): C, 68.49; H, 4.64; N, 18.03; O, 2.94; S, 5.90. Found: C, 68.52; H, 4.61; N, 18.06; O, 2.91; S, 5.93. **9l:** Colorless, (EtOH), yield (70 %), mp 270-272°. *Anal* . Calcd. for $C_{30}H_{22}N_7OSCl$ (564): C, 63.88; H, 3.93; N, 17.38; O, 2.84; S, 5.68. Found: C, 63.85; H, 3.96; N, 17.35; O, 2.81; S, 5.65. **9m:** Orange, (dioxan), yield (74 %), mp 240-243°, ir (KBr): ν (cm^{-1}): 3300, 3240, 3050 (NH,), 3080 (aromatic CH), 1720 (CO), 1620 (C=N) and 1600(C=C); ms: (m/z) (M^+ = 543 (14 %). *Anal* . Calcd. for $C_{31}H_{25}N_7OS$ (543): C, 68.49; H, 4.64; N, 18.03; O, 2.94; S, 5.90. Found: C, 68.53; H, 4.61; N, 18.01; O, 2.91; S, 5.93. **9n:** Orange, (EtOH), yield (65 %), mp 220-223°. *Anal* . Calcd. for $C_{32}H_{27}N_7OS$ (557): C, 68.92; H, 4.88; N, 17.58; O, 2.87; S, 5.75. Found: C, 68.94; H, 4.85; N, 17.55; O, 2.85; S, 5.72. **9o:** Yellow, (EtOH), yield (70 %), mp 290-293°. *Anal* . Calcd. for $C_{31}H_{24}N_7OSCl$ (578): C, 64.41; H, 4.18; N, 16.96; O, 2.77; S, 5.55. Found: C, 64.46; H, 4.16; N, 16.94; O, 2.74; S, 5.52. **9p:** Yellow, (dioxan), yield (82 %), mp 250-253°. *Anal* . Calcd. for $C_{30}H_{22}N_7OSCl$ (564): C, 63.88; H, 3.93; N, 17.38; O, 2.84; S, 5.68. Found: C, 63.85; H, 3.95; N, 17.35; O, 2.80; S, 5.65. **9q:** Yellow, (EtOH), yield (75 %), mp 287—290°. *Anal* . Calcd. for $C_{31}H_{24}N_7OSCl$ (578): C, 64.41; H, 4.18; N, 16.96; O, 2.77; S, 5.55. Found: C, 64.45; H, 4.15; N, 16.94; O, 2.75; S, 5.53. **9r:** Yellow, (dioxan), yield (68 %), mp 300—301°. *Anal* . Calcd. for $C_{30}H_{21}N_7OSCl_2$ (598): C, 60.20; H, 3.54; N, 16.38; O, 2.67; S, 5.36. Found: C, 60.23; H, 3.51; N, 16.36; O, 2.65; S, 5.34.

Synthesis of 3-[(4-substituted-thiazol-2-yl)-hydrazono}-1-aryl-2-(aryl-hydrazono) -propan-1-one derivatives 11a-i:

A mixture of thioamides **5** (0.01 mol) and α-halocompounds **10** (0.01 mol) were stirred in ethano solution at 80 ^{0}C for 3 h. the resulting formed after cooling was collected and crystallized from ethanol to give yellow powdered in good yields.

11a: Yellow, (EtOH), yield (70 %), mp 210—211°, ir (KBr): ν (cm^{-1}): 3300, 3210, 3020 (NH,), 3095 (aromatic CH), 1730 (CO), 1622 (C=N) and 1608(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 2.25 (s, 3H, CH_3), 6.99-8.52 (m, 12H, ArH), 11.50 (s, br, 1H, NH) and 12.50 (s, br, 1H, NH); ms: (m/z) (M^+ = 363 (16 %). *Anal*. Calcd. for $C_{19}H_{17}N_5OS$ (363): C, 62.79; H, 4.71; N, 19.27; O, 4.40; S, 8.82. Found: C, 62.75; H, 4.73; N, 19.25; O, 4.38; S, 8.80. **11b:** Yellow, (EtOH), yield (85 %), mp 250—253°. *Anal*. Calcd. for $C_{20}H_{19}N_5OS$ (377): C, 63.64; H, 5.07; N, 18.55; O, 4.24; S, 8.49. Found: C, 63.61; H, 5.05; N, 18.53; O, 4.20; S, 8.52. **11c:** Yellow, (EtOH), yield (69 %), mp 275—277°. *Anal*. Calcd. for $C_{19}H_{16}N_5OSCl$ (397): C, 57.36; H, 4.05; N, 17.60; O, 4.02; S, 8.06. Found: C, 57.33; H, 4.08; N, 17.63; O, 4.00; S, 8.03. **11d:** Yellow, (EtOH), yield (73 %), mp 260—261°. *Anal*. Calcd. for $C_{24}H_{19}N_5OS$ (425): C, 67.75; H, 4.50; N, 16.46; O, 3.76; S, 7.54. Found: C, 67.72; H, 4.53; N, 16.42; O, 3.73; S, 7.51. **11e:** Colorless, (EtOH), yield (75 %), mp 255—256°. *Anal*. Calcd. for $C_{25}H_{21}N_5OS$ (439): C, 68.32; H, 4.82; N, 15.93; O, 3.64; S, 7.29. Found: C, 68.35; H, 4.85; N, 15.90; O, 3.62; S, 7.26. **11f:** Colorless, (EtOH), yield (70 %), mp 240—242°. *Anal*. Calcd. for $C_{24}H_{18}N_5OSCl$ (459.5): C, 62.67; H, 3.94; N, 15.23; O, 3.48; S, 6.97. Found: C, 62.65; H, 3.91; N, 15.20; O, 3.45; S, 6.95. **11g:** Colorless, (dioxan), yield (80 %), mp 245—247°. *Anal*. Calcd. for $C_{18}H_{15}N_5O_2S$ (365): C, 59.17; H, 4.14; N, 19.17; O, 8.76; S, 8.77. Found: C, 59.20; H, 4.16; N, 19.15; O, 8.74; S, 8.75. **11h:** Yellow, (EtOH), yield (75 %), mp 270—272°, ir (KBr): ν (cm^{-1}): 3360, 3250, 3050 (NH,), 3080 (aromatic CH), 1716 (CO), 1620 (C=N) and 1610 (C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 2.23 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 7.50-8.59 (m, 10H, ArH), 11.10 (s, br, 1H, NH) and 12.80 (s, br, 1H, NH); ms: (m/z) (M^+ = 379 (15 %). *Anal*. Calcd. for $C_{19}H_{17}N_5O_2S$ (379): C, 60.14; H, 4.52; N, 18.46; O, 8.43; S, 8.45. Found: C, 60.10; H, 4.53; N, 18.42; O, 8.40; S, 8.41. **11i:** Yellow, (dioxan), yield (73 %), mp 285—287°. Calcd. for $C_{18}H_{14}N_5O_2SCl$ (399): C, 54.07; H, 3.53; N, 17.51; O, 8.00; S, 8.02. Found: C, 54.09; H, 3.50; N, 17.55; O, 8.03; S, 8.00.

Synthesis of 3-{[4-substituted-5-aryl-hydrazono)-5H-thiazol-2-ylidene]-hydra-zono}-1-aryl-2-(phenyl-hydrazono)-propan-1-one derivatives 13a-i:

13a: Yellow, (EtOH), yield (71 %), mp 240—241°, ir (KBr): ν (cm^{-1}): 3350, 3150 (NH,), 3090 (aromatic CH), 1730 (CO), 1710 (CO), 1617 (C=N) and 1608(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 7.23-8.50 (m, 15H, ArH), 10.50 (s, br, 1H, NH), 11.50 (s, br, 1H, NH) and 13.50 (s, br, 1H, NH); ^{13}C nmr δ (ppm): d = 192.22 (C=O, C-4$^-$)), 185.28 (C=O, C-1), 156.55 (C-5$^-$) 155.22 (C-2), and 137.50.2-118.56 (19 aromatic carbons); ms: (m/z) (M^+ = 469 (10 %). *Anal*. Calcd. for $C_{24}H_{19}N_7O_2S$ (469): C, 61.40; H, 4.08; N, 20.88; O, 6.82; S, 6.83. Found: C, 61.43; H, 4.06; N, 20.85; O, 6.80; S, 6.86. **13b:** Colorless, (EtOH), yield (77 %), mp > 300°. *Anal*. Calcd. for $C_{25}H_{21}N_7O_2S$ (483): C, 62.10; H, 4.38; N, 20.28; O, 6.62; S, 6.63. Found: C, 62.13; H, 4.35; N, 20.25; O, 6.59; S, 6.60. **13c:** Colorless, (EtOH), yield (69 %), mp 295—297°, ir (KBr): ν (cm^{-1}): 3340, 3250 (NH,), 3070 (aromatic CH), 1733 (CO), 1716 (CO), 1619 (C=N) and 1600(C=C); ms (m/z) (M^+= 503 (20 %). *Anal*. Calcd. for $C_{24}H_{18}N_7O_2SCl$ (503.5): C, 57.20; H, 3.60; N, 19.45; O, 6.35; S, 6.36. Found: C, 57.23; H, 3.62; N, 19.42; O, 6.31; S, 6.32. **13d:** Colorless, (EtOH), yield (75 %), mp > 300°. *Anal*. Calcd. for $C_{25}H_{21}N_7O_2S$ (483): C, 62.10; H, 4.38; N, 20.28; O, 6.62; S, 6.63. Found: C, 62.13; H, 4.35; N, 20.25; O, 6.60; S, 6.60. **13e:** Yellow, (EtOH), yield (78 %), mp 250—252°. *Anal*. Calcd. for $C_{26}H_{23}N_7O_2S$ (497): C, 62.76; H, 4.66; N, 19.70; O, 6.43; S, 6.44. Found: C, 62.74; H, 4.64; N, 19.73; O, 6.40; S, 6.42. **13f:** Yellow, (EtOH), yield (70 %), mp >300°. *Anal*. Calcd. for $C_{25}H_{20}N_7O_2SCl$ (518): C, 57.97; H, 3.89; N, 18.93; O, 6.18; S, 6.19. Found: C, 57.95; H, 3.86; N, 18.90; O, 6.15; S, 6.16. **13g:** Yellow, (EtOH), yield (66 %), mp >300°. *Anal*. Calcd. for $C_{24}H_{18}N_7O_2SCl$ (503.5): C, 57.20; H, 3.60; N, 19.45; O, 6.35; S, 6.36. Found: C, 59.20; H, 4.16; N, 19.15; O, 8.74; S, 8.75. **13h:** Colorless, (EtOH), yield (71 %), mp >300°. *Anal*. Calcd. for $C_{25}H_{20}N_7O_2SCl$ (518): C, 57.97; H, 3.89; N, 18.93; O, 6.18; S, 6.19. Found: C, 57.95; H, 3.86; N, 18.95; O, 6.15; S, 6.16. **13i:** Colorless, (EtOH), yield (73 %), mp 285—287°, ir (KBr): ν (cm^{-1}): 3300, 3220 (NH,), 3100 (aromatic CH), 1725 (CO), 1709 (CO), 1614 (C=N) and 1601(C=C); ms: (m/z) (M^+ = 537 (20 %). *Anal*. Calcd. for $C_{24}H_{17}N_7O_2SCl_2$ (538): C, 53.54; H, 3.18; N, 18.21; O, 5.94; S, 5.96. Found: C, 53.51; H, 3.20; N, 18.19; O, 5.91; S, 5.94.

Synthesis of diazocarbodithioate derivatives 15a-c:

An equimolar amount of hydrazoformylketone **3** (0.01 mol), and hydrazinocarbodithioate **14** were stirred in ethanol at room temperature for 3 h. The resulting solid products were collected and crystallized from ethanol to give yellow powdered in very good yields.

15a: Yellow, (EtOH), yield (80 %), mp 212—214°, ir (KBr): ν (cm^{-1}): 3250 (NH,), 3085 (aromatic CH), 1720 (CO), 1617 (C=N) and 1610(C=C); ^{1}H nmr (300 MHz, DMSO) δ_H (ppm): 2.56 (s, 3H, SCH_3), 3.59 (s, 1H, SH), 7.33-8.20 (m, 11H, ArH), 13.10 (s, br, 1H, NH); ^{13}C nmr δ (ppm): d =, 188.28 (C=O, C-1), 166.30 (=C(SH)SCH_3) 164.22 (C-3), 155.50 (C-2) 142.50.2-117.50 (18 aromatic carbons)and 18.00 (SCH_3); ms: (m/z) (M^+ = 356 (12 %). *Anal*. Calcd. for $C_{17}H_{16}N_4OS_2$ (356): C, 57.28; H, 4.52; N, 15.72; O, 4.49; S, 17.99. Found: C, 57.25; H, 4.50; N, 15.70; O, 4.51; S, 18.02. **15b:** Colorless, (EtOH), yield (85 %), mp 225-228°, ir (KBr): ν (cm^{-1}): 3260 (NH,), 3065 (aromatic CH), 1725 (CO), 1622 (C=N) and 1602(C=C); ^{1}H nmr (300 MHz, DMSO) δ_H (ppm): 2.00 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 3.69 (s, 1H, SH), 7.35-8.45 (m, 10H, ArH), 13.50 (s, br, 1H, NH). ^{13}C nmr δ (ppm): d =, 185.28 (C=O, C-1), 165.30 (=C(SH)SCH_3) 162.22 (C-3), 154.50 (C-2) 144.80.2-118.60 (18 aromatic carbons)and in upfield region 18.00 (SCH_3) and 16.89 (CH_3). *Anal*. Calcd. for $C_{18}H_{18}N_4OS_2$ (370): C, 58.35; H, 4.90; N, 15.12; O, 4.32; S, 17.31. Found: C, 58.32; H, 4.92; N, 15.10; O, 4.30; S, 17.30. **15c:** Yellow, (EtOH), yield

(83 %), mp 230—233°. *Anal*. Calcd. for $C_{17}H_{15}N_4OS_2Cl$ (390.5): C, 52.23; H, 3.87; N, 14.33; O, 4.09; S, 16.40. Found: C, 52.20; H, 3.85; N, 14.30; O, 4.12; S, 16.42.

Synthesis of 3-[(5-substututed-3-phenyl-3H-[1,3,4]thiadiazol-2-ylidene)-hydrazono]-1-aryl-2-(phenyl-hydrazono)-propan-1-one derivatives 19a-i:

An equimolar amount of hydrazoformylketone **3** (0.01 mol), the appropriate hydrazonoyl halides **7 a,b** or **12** and triethylamine (0.005 mol) were stirred in ethanol at room temperature for 3 h. The resulting solid products were collected and crystallized from the proper solvent to give orange powdered in very good yields.

19a: Yellow, (EtOH), yield (71 %), mp 240—241°, ir (KBr): ν (cm^{-1}): 3330, 3170 (NH,), 3060 (aromatic CH), 1728 (CO), 1715 (CO), 1619 (C=N) and 1608(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 2.54 (s, 3H, CH_3), 7.33-8.60 (m, 16H, ArH), and 13.50 (s, br, 1H, NH); ms: (m/z) (M^+ = 468 (10 %). *Anal*. Calcd. for $C_{25}H_{20}N_6O_2S$ (468): C, 64.09; H, 4.30; N, 17.94; O, 6.83; S, 6.84. Found: C, 64.06; H, 4.33; N, 17.96; O, 6.85; S, 6.82. **19b:** Colorless, (EtOH), yield (75 %), 220-223 300°, ir (KBr): ν (cm^{-1}): 3330, 3170 (NH,), 3060 (aromatic CH), 1730 (CO), 1720 (CO), 1622 (C=N) and 1600(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 1.88 (s, 3H, CH_3), 2.54 (s, 3H, $COCH_3$), 7.36-8.80 (m, 15H, ArH), and 13.45 (s, br, 1H, NH); ms: (m/z) (M^+ = 482 (8%). *Anal*. Calcd. for $C_{26}H_{22}N_6O_2S$ (482): C, 64.71; H, 4.60; N, 17.42; O, 6.63; S, 6.64. Found: C, 64.74; H, 4.58; N, 17.46; O, 6.60; S, 6.62. **19c:** Colorless, (EtOH), yield (70 %), mp 250-253°, ir (KBr): ν (cm^{-1}): 3350, 3150 (NH,), 3090 (aromatic CH), 1730 (CO), 1710 (CO), 1617 (C=N) and 1608(C=C); ^{1}H nmr (300 MHz, $CDCl_3$) δ_H (ppm): 2.58 (s, 3H, CH_3), 7.41-8.56 (m, 15H, ArH), and 13.39 (s, br, 1H, NH); ^{13}C nmr δ (ppm): d = 195.28 (C=O, $COCH_3$), 189.20 (C=O, C-1), 165.50 (C-2) 163.22 (C-3), 158.45 (C-5), 155.60(C-2), 142.35.2-117.80 (aromatic carbons) and 24.5 (CH_3); ms: (m/z) (M^+ = 469 (13 %). *Anal*. Calcd. for $C_{25}H_{19}N_6O_2SCl$ (502.5): C, 59.70; H, 3.81; N, 16.71; O, 6.36; S, 6.37. Found: C, 59.73; H, 3.84; N, 16.73; O, 6.32; S, 6.39. **19d:** Yellow, (EtOH), yield (80 %), mp 210-213°, ir (KBr): ν (cm^{-1}): 3380, 3250 (NH,), 3110 (aromatic CH), 1732 (CO), 1725 (CO), 1621 (C=N) and 1615(C=C); ms: (m/z) (M^+ = 532 (15 %). *Anal*. Calcd. for $C_{30}H_{22}N_6O_2S$ (530): C, 67.91; H, 4.18; N, 15.84; O, 6.03; S, 6.04. Found: C, 67.93; H, 4.16; N, 15.82; O, 6.00; S, 6.06. **19e:** Yellow, (EtOH), yield (75 %), mp 188-191°. *Anal*. Calcd. for $C_{31}H_{24}N_6O_2S$ (544): C, 68.37; H, 4.44; N, 15.43; O, 5.88; S, 5.89. Found: C, 68.35; H, 4.42; N, 15.40; O, 5.85; S, 5.91. **19f:** Yellow, (EtOH), yield (73 %), mp 230-233°. *Anal*. Calcd. for $C_{30}H_{21}N_6O_2SCl$(564.5): C, 63.77; H, 3.75; N, 14.87; O, 5.66; 5.67. Found: C, 63.75; H, 3.74; N, 14.85; O, 5.63; S, 5.69. **19g:** Yellow, (EtOH), yield (71 %), mp 190-193°, ir (KBr): ν (cm^{-1}): 3390, 3270 (NH,), 3108 (aromatic CH), 1720 (CO), 1680 (CO), 1625 (C=N) and 1606(C=C); ms: (m/z) (M^+ = 500 (11 %). *Anal*. Calcd. for $C_{26}H_{22}N_6O_3S$ (498): C, 62.64; H, 4.45; N, 16.86; O, 9.63; S, 6.43. Found: C, 62.60; H, 4.42; N, 16.85; O, 9.60; S, 6.45. **19h:** Colorless, (EtOH), yield (77 %), mp 210-213°. *Anal*. Calcd. for $C_{27}H_{24}N_6O_3S$ (512): C, 63.27; H, 4.72; N, 16.40; O, 9.36; S, 6.26. Found: C, 63.25; H, 4.70; N, 16.42; O, 9.34; S, 6.23. **19i:** Colorless, (EtOH), yield (69 %), mp 260-263°, ir (KBr): ν (cm^{-1}): 3370, 3220 (NH,), 3060 (aromatic CH), 1720 (CO), 1690 (CO), 1620 (C=N) and 1604(C=C). ^{1}H nmr (300 MHz, DMSO) δ_H (ppm): 1.80 (t, 3H, CH_3, *J* = 7.3 Hz), 4.30 (q, 2H, CH_2 *J* = 7.1 Hz), 7.41-8.56 (m, 15H, ArH), and 13.35 (s, br, 1H, NH); ms: (m/z) (M^+ = 532 (11 %). *Anal*. Calcd. for $C_{26}H_{21}N_6O_3SCl$ (532.5): C, 58.59; H, 3.97; N, 15.77; O, 9.01; S, 6.02. Found: C, 58.62; H, 3.95; N, 15.79; O, 9.04; S, 6.04.

ACKNOWLEDGMENTS

I wish to thank, Prof. A. H. H. Elghandour, Prof. A. O. Abdelhamid, and Prof. G. E. H. Elgemeie, for their guidness assistant to support our collaboration and also F. Lissy at Gottingin University and Ibrahim S. Abdelsalam for microbiological assistant and valuable discussion.

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Source of support: Nil, Conflict of interest: None Declared