Synthesis and Antimicrobial Activity of New Thiazolidine-Based Heterocycles as Rhodanine Analogues

Naglaa A. Abdel Hafez,[a]* Mohamed A. Elsayed,[a] Manal M. El-Shahawi,[b] Ghada E. A. Awad,[c] and Korany A. Ali[a,d]

[a]Applied Organic Chemistry Department, National Research Centre, Dokki, Giza 12622, Egypt
[b]Chemistry Department, Faculty of Science, Ain Shams University, Abbasia, Cairo 11566, Egypt
[c]Chemistry of Natural and Microbial Products Department, National Research Centre, Dokki, Giza 12622, Egypt
[d]Center of Excellence, Advanced Materials and Nanotechnology Group, National Research Centre, Dokki, Giza 12622, Egypt
*E-mail: naglaa1810@gmail.com

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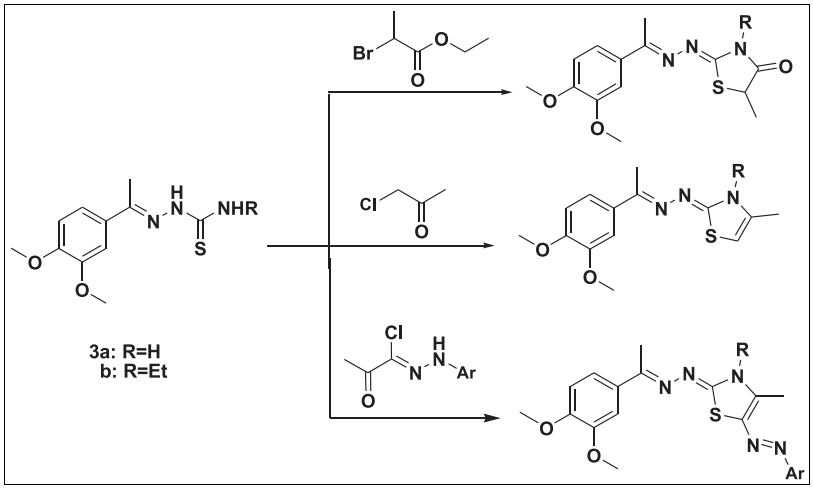


A new series of compounds containing thiazole nucleus as Rhodanine analogues have been synthesized. The new compounds were prepared from the reactions of the thiosemicarbazones (**3a,b**) with a series of α-halo carbonyl compounds to give the corresponding Rhodanine analogues. The thiosemicarbazones derivatives (**3a,b**) were reacted also with hydrazonoyl chlorides to afford the corresponding tri-substituted and tetra-substituted thiazoles. The structures of the newly synthesized compounds were confirmed by elemental analysis and spectral data. The biological activities of the new synthesized Rhodanine analogues' were evaluated for their antimicrobial activities. The results showed that some of these compounds showed excellent activity against two fungal strains, including *Aspergillus niger* and *Aspergillus flavus*, in addition to three yeast strains, including S*accharomyces cervesi, Candida albicans* NRRL Y-477, and *Candida Pathological specimen* compared with the ketoconazol, as the reference drug.

INTRODUCTION

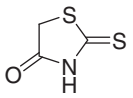
Thiosemicarbazones are a class of organic compounds that used for many decades in medicinal chemistry as they developed as antimicrobial, anticonvulsant, antihelminthic, and anticancer activities [1–5]. On the other hand, thiosemicarbazones consider as a good precursors for the preparation of new class of thiazoles. Moreover, thiazoles as Rhodanine analogues (Fig. 1), in many publications, exhibited a wide range of biological activities such as anti-inflammatory [6], antimicrobial [7,8], anti-apoptotic [9], antioxidant [10], and anticancer [11] properties.

On the other hand, dimethoxy phenyl is an important scaffold in pharmaceutical chemistry with a wide range of registered drugs due to their biological activity. For example, 2,5-dimethoxy-4-chloroamphetamine is a psychedlis drug under a class of drugs known as amphetamines [12].

As part of our targets to synthesize biologically active heterocycles [13,14] and our ongoing interests in the chemistry of hydrazonoyl halides and α-halo carbonyl compounds, we have prepared new series of Rhodanine analogues containing the dimethoxy phenyl scaffold and investigated their biological activities as antifungal agents.

RESULTS AND DISCUSSION

The starting materials for this study, 3,4-dimethoxy acetophenone thiosemicarbazones (**3a,b**), were prepared from the reaction of 3,4-dimethoxyacetophenone with the



Rhodanine

Figure 1. Rhodanine.

thiosemicarbazides (**2a,b**), in the presence of sodium acetate, in refluxing ethanol (Scheme 1).

Thiosemicarbazones have a special interest for the preparation of biologically active ingredients and consider as good precursors for the preparation of novel series of fused thiazole systems. Thus, the thiosemicarbazones (**3a,b**) were treated with the α-halo esters, namely, ethyl bromoacetate and ethyl-2-bromoprpionate, in ethanol and in the presence of equivalent amount of sodium acetate, to afford the corresponding substituted thiazole derivatives **4** and **5a,b,** respectively, (Scheme 2) according to elemental analysis and spectral data. For example, the ^{1}H NMR spectrum of compound **4** showed three singlets signals at δ 2.34, 3.80, and 3.84 ppm because of CH_3, CH_2-thiazole, and $2OCH_3$ groups, respectively. The aromatic and NH protons appeared at 6.98–7.5 and 11.85 ppm, respectively. The structure of compound **4** was confirmed by an independent synthesis via the reaction of the thiosemicarbazones (**3a)** with bromoacetic acid in ethanolic solution of sodium acetate.

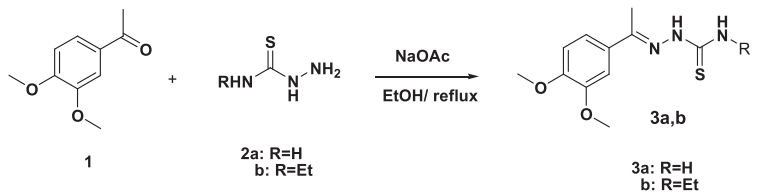
In a similar manner, the thiosemicarbazones (**3a,b**) were treated with chloroacetone and phenacyl chloride to afford the corresponding substituted thiazole derivatives **6a,b** and **7**, respectively (Scheme 3).

The ^{1}H NMR of compound **7**, as example, showed five singlets signals at 2.09, 3.81, 3.91, 6.84, and 7.81 ppm characteristic for CH_3, 2 OCH_3, CH-thiazole, and NH protons, respectively. The mass spectra of compounds **6a,b** and **7** revealed peaks at *m/z*: 291, 319, and 353 corresponding to their molecular ion peaks, respectively.

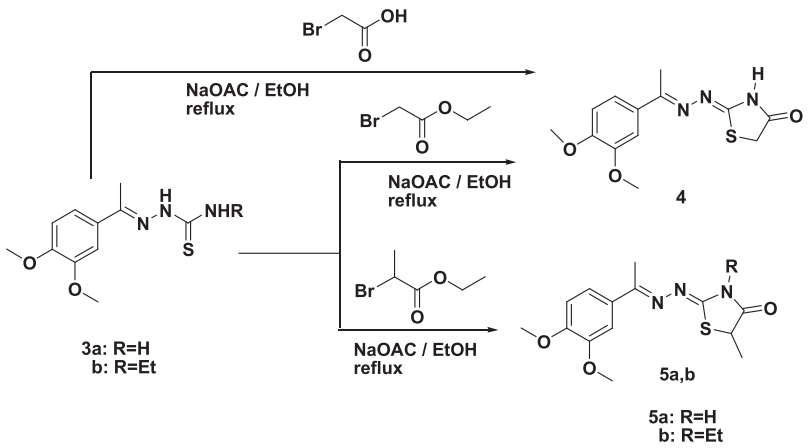
Hydrazonoyl halides are highly versatile active reagents that used for the preparation of different series of substituted pyrazoles and thiazoles [15–18]. Thus herein, we reported the reaction of the thiosemicarbazones (**3a,b**) with two series of hydrazonoyl chlorides to prepare tri-substituted and tetra-substituted thiazoles. Treatment of the thiosemicarbazide derivatives (**3a,b**) with *C*-acetyl-*N*-arylhydrazonoyl chlorides (**8a–c**) in ethanol, and in the presence of catalytic amount of triethylamine, yielded the azo-thiazole derivatives **9a–e** rather than the tautomeric structure **10** (Scheme 4). The ^{1}H NMR and IR spectral data of the products revealed the absence of hydrazinyl NH bands, in addition to the red color of the obtained products because of presence of azo group (-N=N-) proves that the azo-tautomeric structures **9a–e** are the correct and more stable structures.

On the contrary, treatment of the thiosemicarbazide derivatives (**3a,b**) with *C*-ethoxycarbonyl-*N*-arylhydrazonoyl

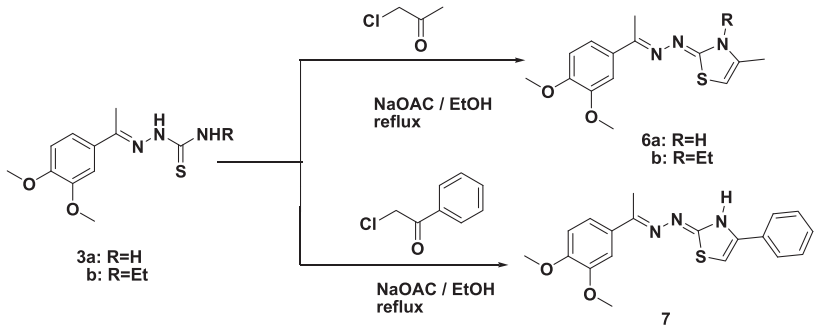
Scheme 1. Synthetic pathway for the formation of compounds **3a,b**.



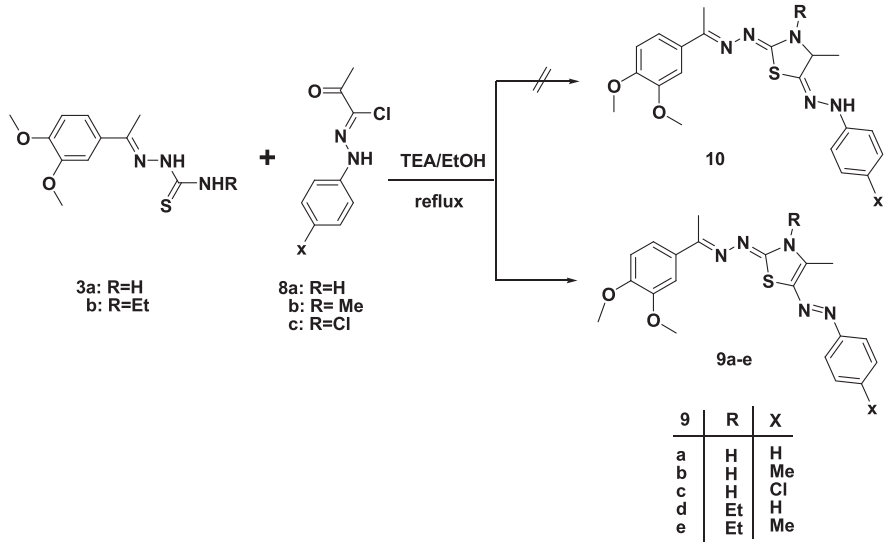
Scheme 2. Synthetic pathway for the formation of compounds **4** and **5a,b**.



Scheme 3. Synthetic pathway for the formation of compounds **6a,b** and **7**.



Scheme 4. Synthetic pathway for the formation of compounds **9a–e**.



9	R	X
a	H	H
b	H	Me
c	H	Cl
d	Et	H
e	Et	Me

chlorides (**11a,b**) afforded the corresponding substituted thiazoles **12a–c** rather than the azo-tautomeric structure **13** (Scheme 5). The structures of compounds **12a–c** were deduced from the corrected analytical and spectroscopic data. For example, the IR spectral data of compounds **12a–c** showed bands at 1713–1715 cm^{-1} because of C=O groups. On the other hand, the colors of the later compounds are pale yellow that refer to the absence of the azo group.

ANTIMICROBIAL ACTIVITY

All the synthesized compounds were tested against a penal of Gram +ve and Gram –ve bacteria, yeast, and fungi. All of the tested compounds showed a neglectable activity against either Gram +ve and Gram –ve bacteria, but some compounds showed considerable highly inhibitory effect against two fungal strains, including *Aspergillus niger* and *Aspergillus flavus,* in addition to three yeast strains, including *Saccharomyces cervesi*, *Candida albicans* NRRL Y-477, and *Candida Pathological specimen*. The compounds **3a**, **3b**, **4**, **5b**, **6b**, **9d**, **9e**, and **12b** exhibited similar or mild better antifungal activity than the reference drug, ketoconazol (Table 1).

MINIMUM INHIBITORY CONCENTRATION

The minimum inhibitory concentration activity of active compounds **3a**, **3b**, **4**, **5b**, **6b**, **9d**, **9e**, and **12b** (represent inhibition zone ≥16 mm) was then evaluated using the twofold serial dilution technique (Table 2). The lowest concentration showing no growth was taken as the minimum inhibitory concentration.

STRUCTURE ACTIVITY RELATIONSHIP

Some of the new compounds showed considerable highly inhibitory effect against two fungal strains and three yeast strains. The compounds **3a**, **3b**, **4**, **5b**, **6b**, **9d**,

Scheme 5. Synthetic pathway for the formation of compounds **12a–c**.

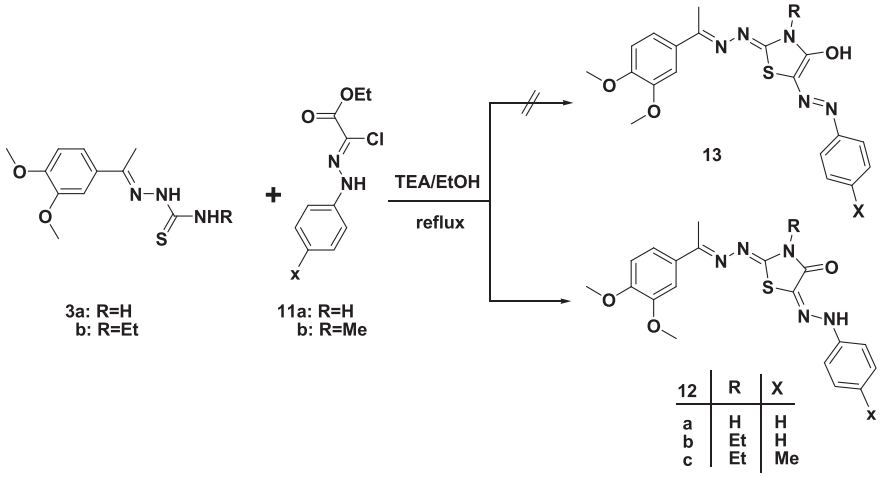


Table 1

The antimicrobial activity expressed, as inhibition diameter zones in millimeters (mm), of the newly synthesized compounds against the pathological strains based on well diffusion assay.

Comp. no	*Aspergillus niger*	*Aspergillus flavus*	*Saccharomyces cervesi*	*Candida albicans* NRRLY-477	*Candida Pathological specimen*
3a	32	33	29	33	30
3b	28	22	25	24	25
4	31	30	28	30	30
5b	30	22	30	28	28
6b	30	30	25	27	29
9d	26	30	25	26	25
9e	32	30	33	31	31
12b	28	29	30	29	30
ketoconazole	33	32	31	31	33

The experiment was carried out in triplicate, and the average zone of inhibition was calculated.

Table 2

Minimum inhibitory concentration (μg/mL) against the pathological strains based on twofold serial dilution technique.

Comp. no.	*Aspergillus Niger*	*Aspergillus flavus*	*Saccharomyces cervesi*	*Candida albicans* NRRLY-477	*Candida Pathological specimen*
3a	65.5	65.5	65.5	65.5	65.5
3b	125	125	125	125	125
4	65.5	65.5	125	125	125
5b	65.5	125	125	125	125
6b	125	65.5	125	125	125
9d	250	125	125	125	125
9e	125	125	65.5	65	65.5
12b	125	125	65.5	65.5	65.6
ketoconazole	65.5	65.5	65.5	65.5	65.5

The experiment was carried out in triplicate, and the average zone of inhibition was calculated.

9e, and **12b** exhibited similar or mild better antifungal activity than the reference drug, ketoconazol. Five of the most active compounds **5b**, **6b**, **9d**, **9e**, and **12b** contain 3-ethyl thiazole scaffold that may lead to enhance the antifungal activity.

EXPERIMENTAL

Chemistry. All melting points were measured on a Gallenkamp melting point apparatus (Weiss Gallenkamp, London, UK). The infrared spectra were recorded in

potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (Pye Unicam Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian, Palo Alto, CA, USA). ^{1}H NMR spectra were run at 300 MHz, and ^{13}C NMR spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6). Chemical shifts are given in parts per million and were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer (Shimadzu) at 70 eV. Elemental analyses were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt, and recorded on Elementar-Vario EL (Germany) automatic analyzer. The reactions were monitored by TLC. Compounds **2b**, **8a–c**, and **11a,b** were prepared according to the reported references [19–22].

Preparation of the thiosemicarbazone derivatives (3a,b). To a mixture of 3,4-dimethoxy acetophenone (**1**) (1.8 g, 10 mmol) and anhydrous sodium acetate (1.64 g, 20 mmol) in absolute EtOH (15 mL), thiosemicarbazide (**2a**) (0.91 g, 10 mmol) or ethyl thiosemicarbazide (**2b**) (1.19 g, 10 mmol) was added. The mixture was refluxed for 3 h, left to cool, then poured into ice water. The formed precipitate was filtered off, dried, and recrystallized from EtOH to afford the corresponding thiosemicarbazones (**3a,b**).

1-(1-(3,4-Dimethoxyphenyl)ethylidene)thiosemicarbazide (3a). The analytical data of compound **3a** were as the reported in the literature [23].

4-Ethyl-1-(1-(3,4-dimethoxyphenyl)ethylidene) thiosemicarbazide (3b). Yellow solid; Yield (72%); mp: 128–129°C (EtOH). IR (KBr, cm^{-1}): *v* 3331 (2NH), 1581(C=N). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.73 (q, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.99 (d, 1H, CH-Ar), 7.22 (s, 1H, CH-Ar), 7.66 (d, 1H, CH-Ar), 7.66 (s, 1H, NH), 8.54 (s, 1H, NH). MS *m/z* (%): 281 [M$^+$] (25), 179 (32), 164 (31), 148 (13), 133 (23), 103 (13). *Anal*. Calcd for $C_{13}H_{19}N_3O_2S$ (281.37): C, 55.49; H, 6.81; N, 14.93; S, 11.40. Found: C, 55.42; H, 6.75; N, 14.87; S, 11.32.

General procedure for the preparation of Rhodanine analogues; 4, 5a,b, 6a,b, and 7. A mixture of the thiosemicarbazones (**3a,b)** (1 mmol) and the appropriate halo compounds including ethyl bromoacetate, ethyl 2-bromopropanoate, chloroacetone, and 2-chloroacetophenone in ethanolic solution of anhydrous sodium acetate (2 mmol) were refluxed for 2–5 h. After cooling, the mixtures were washed with ice cold water. The formed solids were filtered off and dried then crystallized from EtOH to afford the corresponding of Rhodanine analogues, **4**, **5a,b**, **6a,b**, and **7**, respectively.

2-(2-(1-(3,4-Dimethoxyphenyl)ethylidine)hydrazono) thiazolidin-4-one (4). White solid; Yield (87%); mp: 225–227°C (EtOH). IR (KBr, cm^{-1}): *v* 3376 (NH), 1724 (C=O), ^{1}H NMR (DMSO-*d6*): δ 2.34 (s, 3H, CH_3), 3.80, 3.84 (2 s, 8H, $2OCH_3$, CH_2-thiazole), 6.98 (d, 1H, CH-Ar), 7.38 (d, 1H, CH-Ar), 7.50 (s, 1H, CH-Ar), 11.85 (s, 1H, NH). MS *m/z* (%): 293 [M$^+$] (100), 278 (16), 253 (17), 238 (7). *Anal*. Calcd. for $C_{13}H_{15}N_3O_3S$ (293.34): C, 53.23; H, 5.15; N, 14.32; S, 10.93. Found: C, 53.29; H, 5.20; N, 14.36; S, 10.95.

2-(2-(1-(3,4-Dimethoxyphenyl)ethylidine)hydrazono)-5-methylthiazolidin-4-one (5a). Gray solid; Yield (80%); mp: 188–189°C (EtOH). IR (KBr, cm^{-1}): *v* 3372 (NH), 1742 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.68 (d, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.05 (q, 1H, CH-thiazole), 6.86 (d, 1H, CH-Ar), 7.37 (d, 1H, CH-Ar), 7.60 (s, 1H, CH-Ar), 8.45 (br., 1H, NH). MS *m/z* (%): 307 [M$^+$] (100), 292 (16), 163 (3). *Anal*. Calcd. for $C_{14}H_{17}N_3O_3S$ (307.37): C, 54.71; H, 5.57; N, 13.67; S, 10.43. Found: C, 54.77; H, 5.62; N, 13.70; S, 10.45.

2-(2-(1-(3,4-Dimethoxyphenyl)ethylidine)hydrazono)-3-ethyl-5-methylthiazolidin-4-one (5b). White solid; Yield (80%); mp: 150–152°C (EtOH). IR (KBr, cm^{-1}): *v* 1715 (C=O). ^{1}H NMR (DMSO-*d6*): δ 1.21 (t, 3H, CH_3-ethyl), 1.50 (d, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.80 (m, 8H, $2OCH_3$ + CH_2-ethyl), 4.21 (q, 1H, CH-thiazole), 6.99 (d, 1H, CH-Ar), 7.40 (d, 1H, CH-Ar) 7.50 (s, 1H, CH-Ar),. MS *m/z* (%): 335 [M$^+$] (16), 190 (57), 178 (52), 164 (100). *Anal*. Calcd. for $C_{16}H_{21}N_3O_3S$ (335.42): C, 57.29; H, 6.31; N, 12.53; S, 9.56. Found: C, 57.35; H, 6.36; N, 12.56; S, 9.59.

1-(1-(3,4-Dimethoxyphenyl)ethylidine)-2-(4-methylthiazol-2-(3H)-ylidene)hydrazine (6a). Gray solid; Yield (88%); mp: 145–147°C (EtOH). IR (KBr, cm^{-1}): *v* 3542 (NH), 1561 (C=N). ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.22 (s, 1H, CH-thiazole), 6.84 (d, 1H, CH-Ar), 7.20 (d, 1H, CH-Ar), 7.50 (s, 1H, CH-Ar); MS *m/z* (%): 291 [M$^+$] (29), 178 (43), 137 (26), 113 (19), 107 (14). *Anal*. Calcd. for $C_{14}H_{17}N_3O_2S$ (291.37): C, 57.71; H, 5.88; N, 14.42; S, 11.00. Found: C, 57.77; H, 5.93; N, 14.47; S, 11.03.

1-(1-(3,4-Dimethoxyphenyl)ethylidine)-2-(3-ethyl-4-methylthiazol-2-(3H)-ylidene) hydrazine (6b). Yellow solid; Yield (78%); mp: 98–100°C (EtOH). IR (KBr, cm^{-1}): *v* 1595 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3H, CH_3-ethyl), 2.16 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.94 (m, 8H, $2OCH_3$ + CH_2-ethyl), 5.65 (s, 1H, CH-thiazole), 6.83 (d, 1H, CH-Ar), 7.28 (d, 1H, CH-Ar); 7.67 (s, 1H, CH-Ar); MS *m/z* (%): 319 [M$^+$] (91), 178 (19), 164 (66), 149 (46), 128 (39), 114 (33.6). *Anal*. Calcd. for $C_{16}H_{21}N_3O_2S$ (319.42): C, 60.16; H, 6.63; N, 13.16; S, 10.04. Found: C, 60.22; H, 6.68; N, 13.19; S, 10.10.

1-(1-(3,4-Dimethoxyphenyl)ethylidine)-2-(4-phenylthiazol-2-(3H)-ylidene)hydrazine (7). Gray solid; Yield (90%); mp: 188–189°C (EtOH). IR (KBr, cm^{-1}): *v* 3275 (NH), 1562 (C=N). ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.83–7.81 (m, 9H, CH-Ar + CH-thiazole); ^{13}C NMR ($CDCl_3$): δ 12.88, 55.75, 55.85, 103.51, 108.57, 110.42, 118.92, 125.87, 127.66, 128.56, 130.68, 134.78, 146.10, 148.90, 150.09, 151.29, 170.07. MS *m/z* (%): 353 [M^+] (100), 338 (7), 178 (6); *Anal*. Calcd. for $C_{19}H_{19}N_3O_2S$ (353.44): C, 64.57; H, 5.42; N, 11.89; S, 9.07. Found: C, 64.63; H, 5.48; N, 11.94; S, 9.11.

General procedure for the preparation of the azothiazole derivatives 9a–e and 12a–c. To a mixture of thiosemicarbazones (**3a,b)** (1 mmol) and the appropriate hydrazonoyl chlorides (1 mmol) in EtOH, TEA (1 mmol) was added. The reaction mixture was then refluxed for 6–8 h. After cooling, the mixture was washed with ice cold water. The formed solids were filtered and dried then crystallized from EtOH to afford the corresponding azo-thiazole derivatives **9a–e** and **12a–c**, respectively.

1-(1-(3,4-Dimethoxyphenyl)ethylidine)-2-(4-methyl-5-phenylazo-thiazole-2-(3H)-ylidene)hydrazine (9a). Reddish solid; Yield (92%); mp: 125–127°C (EtOH). IR (KBr, cm^{-1}): *v* 3348 (NH), 1597 (C=N). ^1H NMR ($CDCl_3$): δ 2.54 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.85–7.64 (m, 8H, CH-Ar); ^{13}C NMR ($CDCl_3$): δ 15.45, 16.61, 55.85, 55,.97, 109.73, 114.08, 121.03, 122.69, 125.70, 129.36, 130.50, 140.57, 142.66, 148.70, 151.46, 165.18, 169.42, 171.31. MS *m/z* (%): 395 [M^+] (7), 353 (100), 337 (12), 292 (4). *Anal*. Calcd. for $C_{20}H_{21}N_5O_2S$ (395.48): C, 60.74; H, 5.35; N, 17.71; S, 8.11. Found: C, 60.70; H, 5.39; N, 17.65; S, 8.15.

1-(1-(3,4-Dimethoxyphenyl)ethylidine)-2-(4-methyl-5-(4-methylphenylazo)-thiazole-2-(3H)-ylidene)hydrazine (9b). Reddish solid; Yield (94%); mp: 215–217°C (EtOH). IR (KBr, cm^{-1}): *v* 3376 (NH), 1600 (C=N). ^1H NMR (DMSO-*d6*): δ 2.27 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.84 (m, 9H, $2OCH_3$ + CH_3), 3.85 (s, 3H, OCH_3), 6.92–8.20 (m, 7H, CH-Ar), 10.05 (s, 1H, NH, exchangeable with D_2O); MS *m/z* (%): 409 [M^+] (2), 305 (1), 113 (18), 101 (16). *Anal*. Calcd. for $C_{21}H_{23}N_5O_2S$ (409.50): C, 61.59; H, 5.66; N, 17.10; S, 7.83; Found: C, 61.65; H, 5.73; N, 17.13; S, 7.86.

1-(1-(3,4-Dimethoxyphenyl)ethylidine)-2-(4-methyl-5-(4-chlorophenylazo-thiazole-2-(3H)-ylidene)hydrazine (9c). Dark red solid; Yield (89%); mp: 228–230°C (EtOH). IR (KBr, cm^{-1}): *v* 3376 (NH), 1598 (C=N). ^1H NMR (DMSO-d_6): δ 2.26 (s, 3H, CH_3), 3.78–3.82 (m, 9H, $2OCH_3$ + CH_3), 6.92–8.20 (m, 7H, CH-Ar), 10.05 (s, 1H, NH). MS *m/z* (%): 429 [M^+] (5), 425 (100), 353 (52), 252 (47), 236 (30), 178 (7). *Anal*. Calcd. for $C_{20}H_{20}ClN_5O_2S$ (429.10): C, 55.87; H, 4.69; N, 16.29; S, 7.46; Found: C, 55.94; H, 4.74; N, 16.32; S, 7.49.

1-(1-(3,4-Dimethoxyphenyl)ethylidine)-2-(3-ethyl-4-methyl-5-phenylazo-thiazole-2-ylidene)hydrazine (9d). Red solid; Yield (89%); mp: 186–188°C (EtOH). IR (KBr, cm^{-1}): *v* 1595 (C=N), 2934 (CH aliphatic). ^1H NMR ($CDCl_3$) δ 1.37 (t, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.15 (q, 2H, CH_2), 6.99–7.69 (m, 8H, CH-Ar). MS *m/z* (%): 425 [M^+] (5), 410 (11), 341 (12), 296 (14), 178 (35), 164 (53), 104 (26), 91 (45). *Anal*. Calcd. for $C_{22}H_{25}N_5O_2S$ (423.53): C, 62.39; H, 5.95; N, 16.54; S, 7.57. Found: C, 62.31; H, 5.86; N, 16.50; S, 7.51.

1-(1-(3,4-Dimethoxyphenyl)ethylidine)-2-(3-ethyl-4-methyl-5-(4-methylphenylazo)-thiazole-2-ylidene)hydrazine (9e). Red solid; Yield (79%); mp: 195–197°C (EtOH). IR (KBr, cm^{-1}): *v* 1587 (C=N). ^1H NMR ($CDCl_3$): δ 1.44 (t, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.45 (q, 2H, CH_2), 6.90–7.95 (m, 7H, CH-Ar). MS *m/z* (%): 437 [M^+] (2), 425 (4), 413 (23), 356 (42), 301 (11), 177 (8), 137 (34). 85 (100). *Anal*. Calcd. for $C_{23}H_{27}N_5O_2S$ (437.56): C, 63.13; H, 6.22; N, 16.01; S, 7.33; Found: C, 63.19; H, 6.27; N, 16.06; S, 7.35.

2-(2-(1-(3,4-Dimethoxyphenyl)ethylidine)hydrazono)-5-phenylazo-thiazolidin-4-one (12a). Pale yellow solid; Yield (79%); mp: 163–165°C (EtOH). IR (KBr, cm^{-1}): *v* 3118 (NH), 1713 (C=O); MS *m/z* (%): 397 [M^+] (11), 305 (1), 289 (0.7), 113 (20.5), 101 (18). *Anal*. Calcd. for $C_{19}H_{19}N_5O_3S$ (397.45): C, 57.42; H, 4.82; N, 17.62; S, 8.07; Found: C, 57.37; H, 4.75; N, 17.57; S, 8.01.

2-(2-(1-(3,4-Dimethoxyphenyl)ethylidine)hydrazono)-3-ethyl-5-phenylazo-thiazolidin-4-one (12b). Pale yellow solid; Yield (79%); mp: 170–172°C (EtOH). IR (KBr, cm^{-1}): *v* 3107 (NH), 1717 (C=O). ^1H NMR ($CDCl_3$): δ 1.43 (t, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.44 (q, 2H, CH_2), 6.85–8.10 (m, 8H, CH-Ar). ^{13}C NMR ($CDCl_3$): δ 14.11, 14.69, 55.85, 62.79, 109.10, 110.29, 110.38, 119.80, 120.02, 121.94, 126.67, 128.73, 130.81, 131.42, 139.4, 148.80, 150.53, 157.03, 159.2, 160.05, 164.01. MS *m/z* (%): 425 [M^+] (62), 355 (55), 341 (100), 299.9 (17), 178 (6), 164 (18), 148.9 (5). *Anal*. Calcd. for $C_{21}H_{23}N_5O_3S$ (425.50): C, 59.28; H, 5.45; N, 16.46; S, 7.54. Found: C, 59.19; H, 5.39; N, 16.38; S, 7.46.

2-(2-(1-(3,4-Dimethoxyphenyl)ethylidine)hydrazono)-5-(4-methylphenylazo)-thiazolidin-4-one (12c). Pale yellow solid; Yield (69%); mp: 155–158°C (EtOH). IR (KBr, cm^{-1}): *v* 3376 (NH), 1710 (C=O). ^1H NMR ($CDCl_3$): δ 1.42 (t, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.48 (q, 2H, CH_2), 6.87–7.95 (m, 7H, CH-Ar). MS *m/z* (%): 440 [M^+ + 1] (90), 439 (9), 355 (100), 341 (97), 300 (9). *Anal*. Calcd. for $C_{22}H_{25}N_5O_3S$ (439.53): C, 60.12; H, 5.73; N, 15.93; S, 7.30. Found: C, 60.15; H, 5.77; N, 15.87; S, 7.33.

Antimicrobial activity. All synthesized chemical compounds were individually tested against a panel of Gram +ve and Gram –ve bacterial pathogens, yeast, and fungi. Antimicrobial tests were carried out by the agar well diffusion method [24] using 100 µL of suspension as inoculum containing 1×10^6 CFU/mL of pathogenic bacteria that include *Staphelococcus aureus* ATCC29213, *Bacillus subtilis* ATCC6633 as a Gram + ve bacteria, *Escherichia coli* ATCC2592, *Pseudomonas aeroginosa* ATCC27953 as a Gram –ve bacteria, 1 × 106 CFU/mL yeast that include *S*. *cervesi*, *C*. *albicans* NRRL Y-477, and *C*. *albicans* isolated from pathological sample, and 1×10^4 spore/mL of fungi that include *A*. *niger* and *A*. *flavus*. The tested microorganism's inoculums were spread on a sterile Petri dishes containing Müller–Hinton agar. After the media had cooled and solidified, wells (10 mm in diameter) were made in the solidified agar and loaded with 100 µL of tested compound solution prepared by dissolving 10 mg of the chemical compound in 1 mL of DMSO. The inculcated plates were then incubated for 24 h at 37°C for bacteria and yeast and 48 h at 28°C for fungi. Negative controls were prepared using DMSO employed for dissolving the tested compound. Ten milligrams per milliliters of Ketoconazole was used as standard for antifungal activity. After incubation time, antifungal activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. The observed zone of inhibition is presented in Table 1. Antimicrobial activities were expressed as inhibition diameter zones in millimeters (mm). The experiment was carried out in triplicate, and the average zone of inhibition was calculated.

Minimum inhibitory concentration measurement. Twofold serial dilutions of the tested compounds solutions were prepared using the proper nutrient broth [25]. The final concentrations of the solutions were 500, 250, 125, and 65.5 µg/mL. The tubes were then inoculated with the test organisms, grown in their suitable broth at 37°C for 24 h for tested microorganisms (1×10^6 CFU/mL for yeast and 1×10^4 spore/mL for fungi), and each 5 mL received 0.1 mL of the above inoculum and incubated at 37°C for 24 h.

CONCLUSION

In conclusion, we have prepared a series of Rhodanine analogues from the reaction of thiosemicarbazone derivatives with α-halo carbonyl compounds and hydrazonoyl chlorides to afford a series of highly functionalized thiazole derivatives in good yields. Some of the new synthesized Rhodanine analogues' were showed excellent activity against yeast and fungi strains compared with ketoconazol, as reference drug.

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