Design, synthesis, characterization and antimicrobial evaluation of some novel hydrazinecarbothioamide, 4-thiazolidinone and 1,2,4-triazole-3-thione derivatives

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Abstract

A series of novel hydrazinecarbothioamide (**5a,c,f**), 4-thiazolidinone (**6a-e**), and 1,2,4-triazole-3-thione (**7a-d**) were designed and synthesized. The structural elucidations of the novel compounds were performed by IR, ^{1}H-NMR, ^{13}C-NMR, mass and elemental analysis. All novel derivatives were evaluated for their antibacterial and antifungal activities against 9 diverse microorganisms. According to the biological activity studies of the compounds, **6d**, **7c** and **7d** displayed hope promising antibacterial activity. Furthermore, **6d** displayed potent antifungal activity. Consequently, the obtained results revealed that **6d**, **7c** and **7d** present a leading structure for future drug development due to its straightforward synthesis and relevant bioactivity.

KEYWORDS synthesis, structure elucidation, hydrazinecarbothioamide, 4-thiazolidinone, 1,2,4-triazole-3-thione, antimicrobial activity,

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1 INTRODUCTION

The sharply rising level of antibiotic-resistant bacterias, which was speeded up by the misuse of antibiotics, has become a significant and global health problem.[1] Day by day, an increasing number of infection based diseases caused by resistant bacterias have been failing to respond to conventional treatment and in some cases, even last-resort antibiotics have lost their curative effect.[2] Besides that, infections stemming from fungal microorganisms have been continuing to increase swiftly because of the enormous number of immunocompromised patients and easily gained resistance.[3, 4] Since the sharply rising level of multi-drug resistant microorganisms, the discovery of novel compounds to overcome these microorganisms has become one of the major issues of pharmaceutical chemistry today.[5]

Triazoles are members of heterocyclic compounds possessing a five-membered ring, that bears two carbon atoms and three nitrogen atoms.[6,7] Triazole derivatives have attracted the interest of researchers due to their wide range of biologic activities like anticonvulsant,[8] antidepressant,[9] antioxidant,[10] anti-inflammatory,[11] analgesic,[12] antinociceptive,[13] antibacterial,[14-16] antimycobacterial,[17] antifungal,[15,16,18,19] antiviral,[20] anticancer,[21,22] anti-parasitic,[23] 5α-reductase inhibitory,[24] and anti-urease,[25] . Also, there are known drugs which are currently being used in the treatment and contain 1,2,4-triazole moiety like fluconazole (antifungal), itraconazole (antifungal), voriconazole (antifungal), rizatriptan (5-hydroxytryptamine 1 receptor subtype agonist/migraine) and ribavirin (antiviral) (Figure 1).

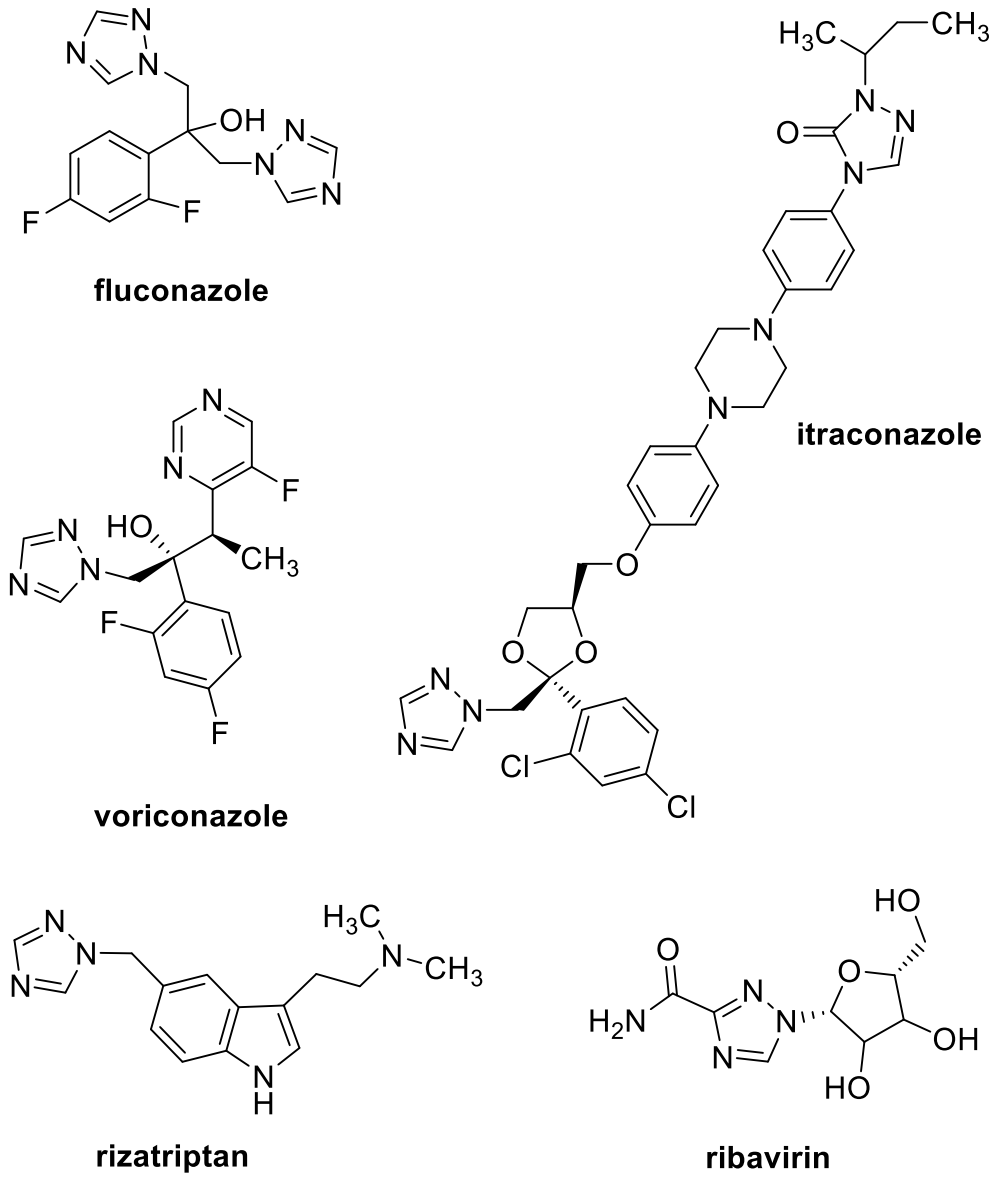

Figure 1 Chemical structures of some drugs bearing 1,2,4-triazole moiety

4-Thiazolidinones are thiazolidine derivatives which possess a sulfur atom at position one, a nitrogen atom at position three, and a carbonyl group at position four. 4-Thiazolidinones have been considered as a pharmacologically active scaffold due to their wide range of reported biological activities in literature. The compounds bearing 4-thiazolidinone moiety have been reported in the literature by their antibacterial,[26] antifungal,[27,28] antitubercular,[29] anticancer,[30-33] anti-inflammatory,[34] analgesic,[35] anticonvulsant,[36] antiviral,[37,38] cytotoxic,[39] and antidiabetic[40] activities. Compounds such as ralitoline (anticonvulsant), pioglitazone (hypoglycemic) and thiazolidomycin (activity against Streptomyces species), based on 4-thiazolidinone pharmacophore are already in clinical use as commercial products (Figure 2).

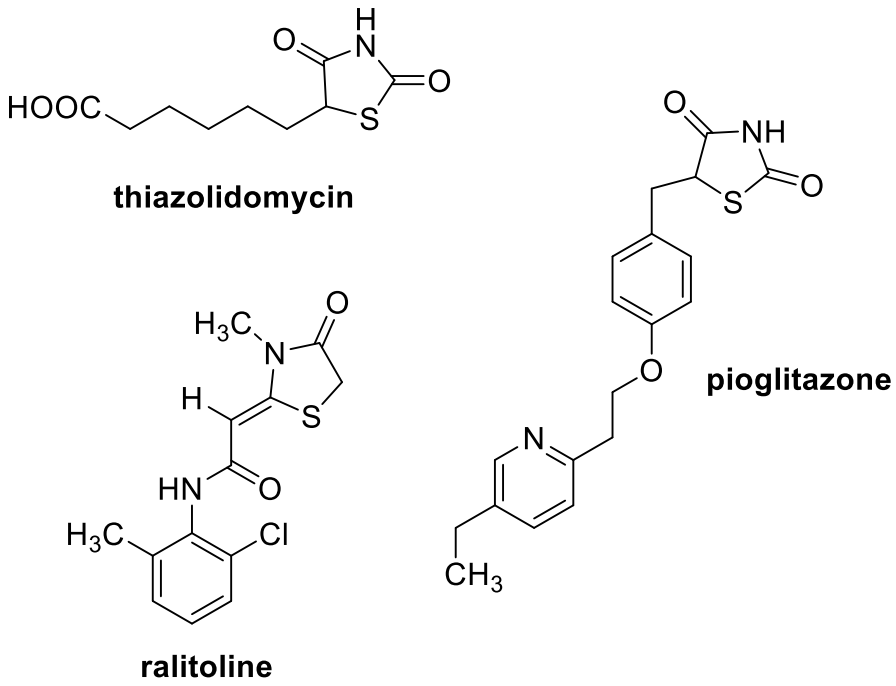

Figure 2 Chemical structures of some drugs bearing 4-thiazolidinone moiety

Thiosemicarbazide moiety bearing compounds have been considered as biologically important since their wide range of reported biological activity such as antibacterial,[41,42] antifungal,[43] antitubercular,[44] anticonvulsant,[45] anticancer,[46,47] cytotoxic[42] and antioxidant[48]. Thiosemicarbazide moiety is not only important because of their potential activity but also their ability to be used as starting compounds for the synthesis of diverse biologically potent moieties such as 1,2,4-triazole-3-thiones,[48] 4-thiazolidinones,[49] 1,3,4-oxadiazoles[11] and 1,3,4-thiadiazoles.[11] Antitubercular thioacetazone, anticancer triapine and methisazone are drug molecules that are used in treatment currently and bearing thiosemicarbazide/thiosemicarbazone moiety (Figure 3).

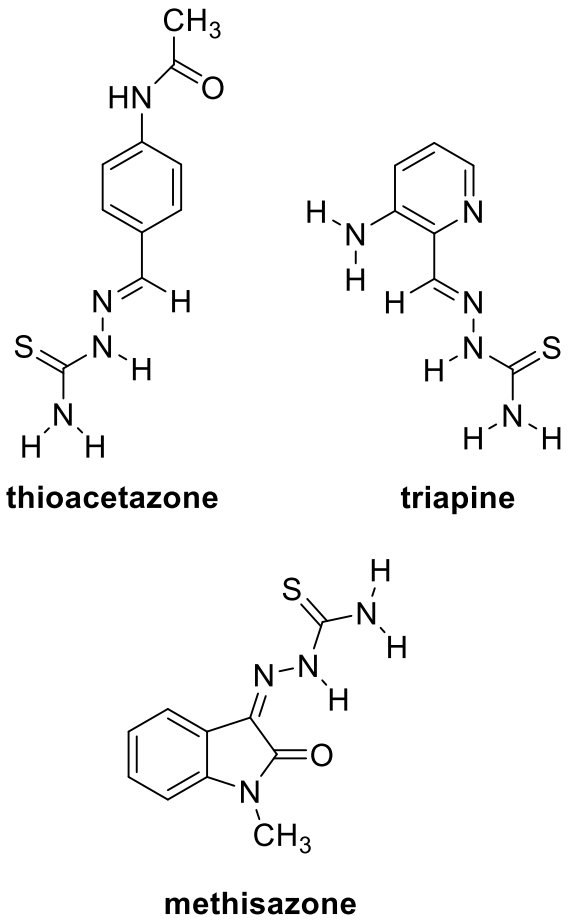

Figure 3 Chemical structures of some drugs bearing thiosemicarbazide/thiosemicarbazone moiety

In this study, the design, synthesis, structure elucidation, antibacterial and antifungal activity studies of novel thiosemicarbazide, 1,2,4-triazole and 4-thiazolidinone derivatives were reported. Structural characterizations of the synthesized compounds were performed by IR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry and elemental analysis. Antibacterial activities of the synthesized compounds were evaluated against *S. aureus* (ATCC 29213), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC27853). Besides that, antifungal activities of the novel compounds were evaluated against *C. albicans* (ATCC10231), *C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019), *M. gypseum* (NCPF580), *T. metagrophytes var. erinacei* (NCPF 375) and *T. tonsurans* (NCPF 245).

2 RESULTS AND DISCUSSION

2.1 Chemistry

The title compounds (**5a**, **5c**, **5f**, **6a-e** and **7a-d**) (Table 1) were synthesized from furoic acid hydrazide by a five and six-step synthesis through the pathways displayed in Figure 4 and Figure 5. Furoic acid hydrazide and 4-bromophenyl isothiocyanate were refluxed in ethanol to yield *N*-(4-bromophenyl)-2-(furan-2-carbonyl)hydrazinecarbothioamide (**1**). Thereafter, a solution of compound **1** in 2N aqueous NaOH was refluxed. After cooling, the reaction mixture was acidified by 12.5% aqueous HCI and thus 4-(4-bromophenyl)-5-(furan-2-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**2**) was obtained. Compound **2** and ethyl bromoacetate were refluxed in ethanol in the presence of KOH to obtain ethyl 2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (**3**). By heating compound **3** and hydrazine hydrate in ethanol, 2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetohydrazide (**4**) was yielded. The compound **4** and substituted isothiocyanates were refluxed in ethanol to yield 2-(2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-(alkyl/allyl/aryl)hydrazinecarbothioamides (**5a-f**). **5a-f**, ethyl bromoacetate and fused sodium acetate were refluxed in ethanol to yield 2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N'*-(3-(alkyl/allyl/aryl)-4-oxothiazolidin-2-ylidene)acetohydrazides (**6a-e**). **5a-f** were heated in 2N aqueous NaOH under reflux. After cooling, the reaction mixture was acidified by 12.5% aqueous HCI and in this way 5-(((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-4-(alkyl/allyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (**7a-d**) were yielded. The reaction yields of the novel compounds **5a**,**c**,**f**, **6a-e** and **7a-d** were between the interval of 99.50%-83.23%, 97.14%-81.74% and 98.75%-75.70% respectively.

When the chemical structures of the synthesized compounds were examined, it was observed that there is just one carbonyl group belonging **5a**,**c**,**f** which is found in the hydrazide functional group of the mentioned compounds. Besides that, there are two carbonyl groups, which are found in the hydrazone moiety and 4-thiazolidinone moiety of **6a-e**. Moreover, there is no carbonyl group belonging **7a-d**. Also according to the IR spectroscopy results, the stretching bands belonging to the carbonyl groups of hydrazide functional group of **5a**,**c**,**f** were able to be observed in the range of 1710-1688 cm^{-1} and there wasn't a secondary carbonyl peak belonging a secondary carbonyl group. Moreover, the stretching bands belonging to the carbonyl groups of hydrazone moiety and 4-thiazolidinone ring of **6a-e** were

in the range of 1684-1645 cm^{-1} and 1727-1716 cm^{-1} respectively. No band belonging to a carbonyl group was observed for **7a-d**.

The IR values belonging to the mentioned carbonyl groups of **5a**,**c**,**f** and **6a-e** were in agreement with the literature.[49-52]

According to the literature, N-H proton belonging the hydrazide group of compound **4** was observed in 9.48 ppm as a broad singlet and also the NH_2 protons were observed in 3.45 ppm as a broad singlet. When the results obtained from compound **5a**,**c**,**f** were examined, it was determined that the peaks of NH_2 protons were disappeared and totally three diverse N-H proton were observed in the region of 10.30-8.16 ppm. This results indicated the formation of thiosemicarbazide derivatives from compound **3**. N-H peak of **6a-e** and **7a-d** were observed in the range of 10.56 – 10.49 and 13.69-13.58 ppm respectively and just one N-H peak was observed for each of the mentioned compounds. Decreasing of the number of N-H peaks from three to one, indicated the formation of **6a-e** and **7a-d** from **5a-e**. The peaks of SCH_2 protons of **5a**,**c**,**f** and **7a-d** were determined in the range of 4.09-3.88 and 4.36-4.33 ppm respectively. The peak integration values of the mentioned SCH_2 peaks were 2H since there is just one SCH_2 group belonging **5a**,**c**,**f** and **7a-d**. The SCH_2 protons belonging **6a-e** were determined in the range of 4.17-3.95 ppm. Unlike **5a**,**c**,**f** and **7a-d**, the integration value of the SCH_2 peaks of **6a-e** were determined as 4H since there are two diverse SCH_2 group in **6a-e**.

The IR, ^1H NMR, ^{13}C NMR and mass spectra of the novel compounds were in compliance with the assigned structures and the literature.[49-52] No unacceptable side reactions were observed, and the desired products were obtained in moderate to good yields.

Table 1 Some physicochemical and analytical data of the compounds bearing thiosemicarbazide (**5a-f**), 4-thiazolidinone (**6a-e**) and 1,2,4-triazole-3-thione (**7a-d**) moiety

Compound	R	Formula (MW)	M.p. (^{o}C)	Yield (%)
5a	CH_3	$C_{16}H_{15}BrN_6O_2S_2$ (467.37)	176-177	93.92
5c	C_3H_7	$C_{18}H_{19}BrN_6O_2S_2$ (495.42)	203-204	83.23
5f	$C_6H_4CH_3$(4-)	$C_{22}H_{19}BrN_6O_2S_2$ (543.46)	185-186	99.50
6a	CH_3	$C_{18}H_{15}BrN_6O_3S_2$ (507.39)	222-223	81.74
6b	C_2H_5	$C_{19}H_{17}BrN_6O_3S_2$ (521.42)	164-165	97.14
6c	C_3H_7	$C_{20}H_{19}BrN_6O_3S_2$ (535.44)	171-172	88.11
6d	CH_2-CH=CH_2	$C_{20}H_{17}BrN_6O_3S_2$ (533.43)	174-175	88.23
6e	C_6H_5	$C_{23}H_{17}BrN_6O_3S_2$ (569.46)	222-223	82.35
7a	CH_3	$C_{16}H_{13}BrN_6OS_2$ (449.35)	218-220	75.70
7b	C_2H_5	$C_{17}H_{15}BrN_6OS_2$ (463.38)	258-259	93.28
7c	C_3H_7	$C_{18}H_{17}BrN_6OS_2$ (477.41)	263-264	92.78
7d	CH_2-CH=CH_2	$C_{18}H_{15}BrN_6OS_2$ (475.39)	249-250	98.75

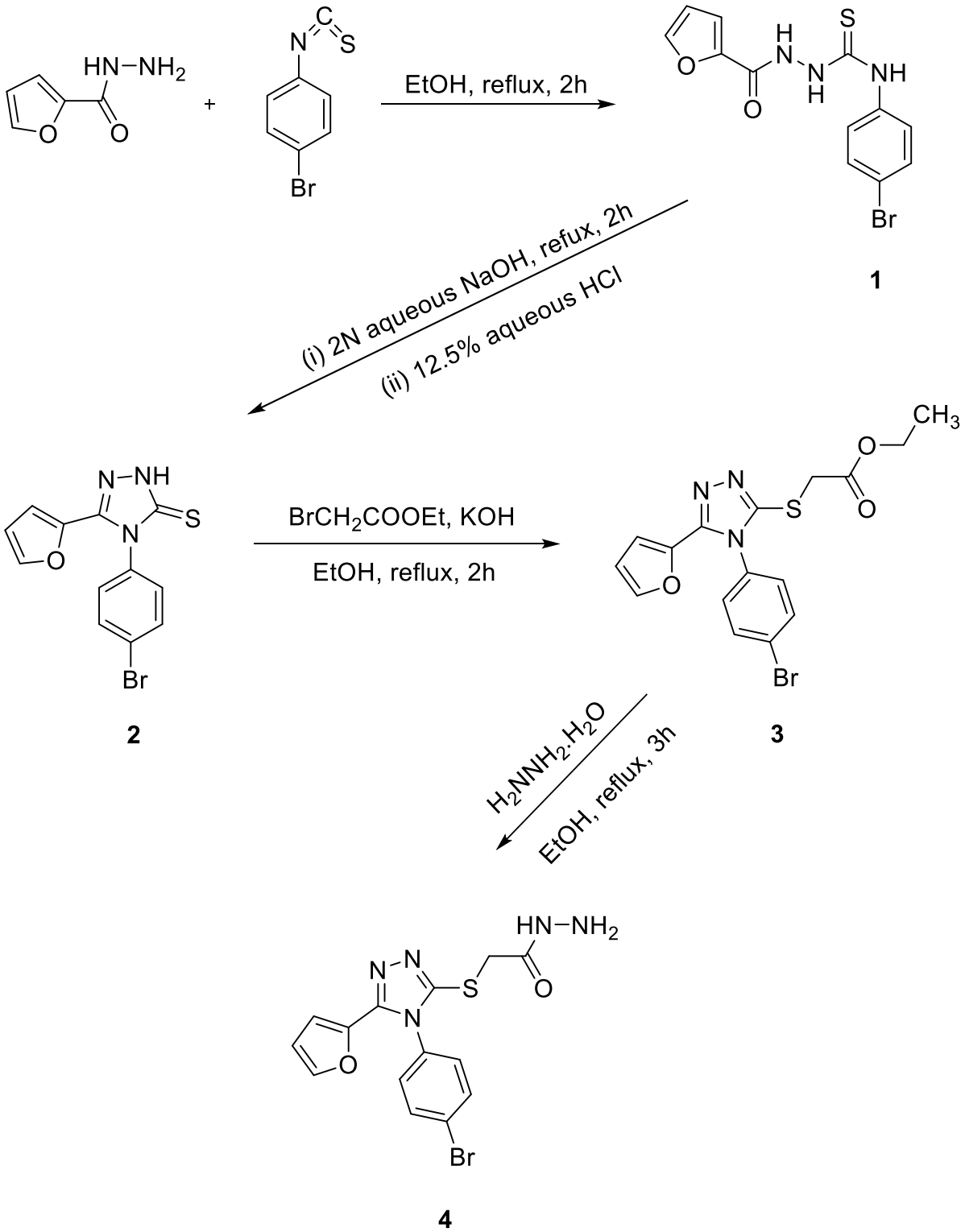

Figure 4 Synthesis of the starting compounds **1**, **2**, **3** and **4**

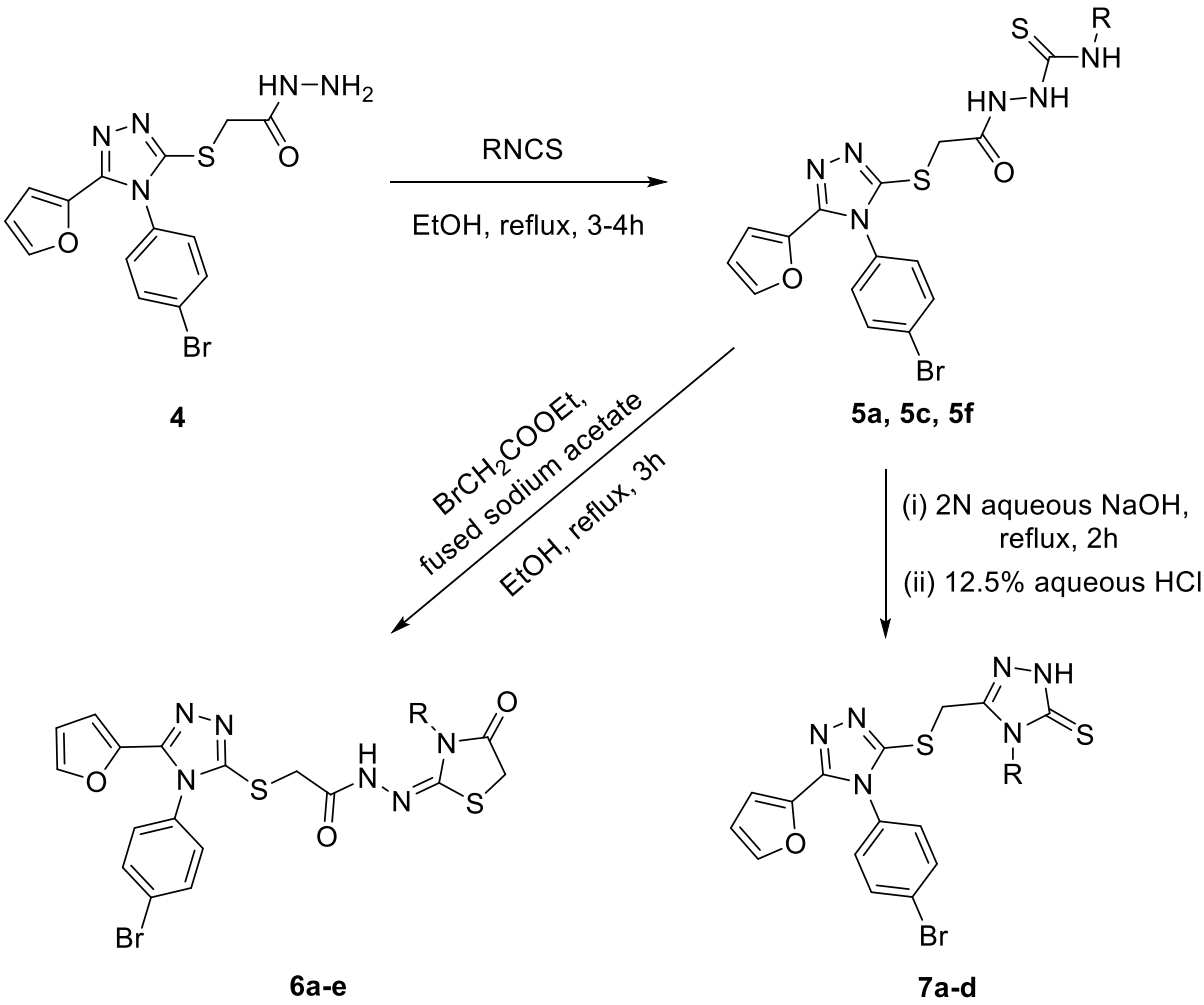

Figure 5 Synthesis of the title compounds

2.2 Biological activity

All of the title compounds were evaluated for *in vitro* antibacterial activity against *S. aureus* ATCC 29213, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 as well as for antifungal activity against *C. albicans* ATCC 10231, *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *M. gypseum* NCPF580, *T. mentagrophytes var. erinacei*, *T. tonsurans* NCPF245 using the microbroth dilution method (Table 2, Table 3). As can be seen in Table 1, **6d** (R = CH_2-CH=CH_2), **7c** (R = C_3H_7) and **7d** (R = CH_2-CH=CH_2) showed the highest activity against *S. aureus* ATCC 29213 (MIC = 32 µg/mL). Besides, **7c** (R = C_3H_7) and **7d** (R = CH_2-CH=CH_2) displayed the highest activity against *E. coli* ATCC 25922 (MIC = 32 µg/mL). In addition, **7d** (R = CH_2-CH=CH_2) displayed the highest activity against *P. aeruginosa* ATCC 27853 (MIC = 32 µg/mL). Generally, 1,2,4-triazole-3-thione derivatives displayed higher antibacterial activity than thiosemicarbazide and 4-thiazolidinone derivatives against *S. aureus* ATCC

29213, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. Propyl and allyl substitution of 4-position of the 1,2,4-triazole-3-thione ring increased the antibacterial activity. Besides, 3-allyl substitution of 4-thiazolidinone ring increased the antibacterial activity of 4-thiazolidinone derivatives. This indicated the importance of the mentioned *N*-allyl substitutions for antibacterial activity of 1,2,4-triazole-3-thione and 4-thiazolidinone derivatives.

Table 2 Antibacterial activity of the title compounds (**5a,c,f**, **6a-e**, **7a-d**) (MIC µg/mL)

Compound	Microorganisms[a]		
	A	B	C
5a	> 64	64	64
5c	> 64	> 64	> 64
5f	64	> 64	> 64
6a	> 64	> 64	> 64
6b	> 64	64	> 64
6c	> 64	64	> 64
6d	32	64	64
6e	64	> 64	> 64
7a	64	64	64
7b	> 64	64	> 64
7c	32	32	64
7d	32	32	32
Levofloxacin	0.12	0.015	0.5

[a] A = *S. aureus* ATCC 29213, B = *E. coli* ATCC 25922, C = *P. aeruginosa* ATCC 27853

6d was determined as the most active compound against *C. albicans* ATCC 10231 (MIC = 16 µg/mL), *C. parapsilosis* ATCC 22019 (MIC = 8 µg/mL), *T. mentagrophytes var. erinacei* NCPF375 (MIC = 8 µg/mL) and *T. tonsurans* NCPF245 (MIC = 8 µg/mL). **6c**, **6d**, **7c** and **7d** displayed the highest activity against *C. krusei* ATCC 6258 (MIC = 16 µg/mL). **6a**, **6b**, **6d**, **7a**, **7c** and **7d** displayed the highest activity against *M. gypseum* NCPF580 (MIC = 16 µg/mL). Generally, 1,2,4-triazole-3-thione and 4-thiazolidinone derivatives displayed higher

antifungal activity than thiosemicarbazide derivatives. Besides, the most active antifungal compound was

determined as **6d** (MIC = 16 μg/mL for *C. albicans* ATCC 10231, MIC = 16 μg/mL for *C. krusei* ATCC 6258, MIC = 8 μg/mL for *C. parapsilosis* ATCC 22019, MIC = 16 μg/mL for *M. gypseum* NCPF580, MIC = 8 μg/mL for *T. mentagrophytes var. erinacei* NCPF375 and *T. tonsurans* NCPF245), which has an allyl group at the 3-position of the 4-thiazolidinone ring. This indicated that, 3-allyl substitution of 4-thiazolidinone ring is not only important for their antibacterial activity but also their antifungal activity.

Table 3 Antifungal activity of the title compounds (**5a**,**c**,**f**, **6a-e**, **7a-d**) (MIC μg/mL)

Compound	Microorganisms[a]					
	A	B	C	D	E	F
5a	32	32	32	32	16	16
5c	32	32	32	32	32	32
5f	64	32	64	64	32	32
6a	32	32	16	16	16	16
6b	64	32	32	16	16	16
6c	32	16	16	32	16	32
6d	16	16	8	16	8	8
6e	32	64	64	32	64	64
7a	32	32	32	16	16	16
7b	64	64	64	64	64	64
7c	32	16	16	16	16	16
7d	32	16	16	16	32	16
Itraconazole	0.12	0.12	0.06	n.t.	n.t.	n.t.
Amphotericin B	n.t.	n.t.	n.t.	0.5	0.5	0.25

[a] A = *C. albicans* ATCC 10231, B = *C. krusei* ATCC 6258, C = *C. parapsilosis* ATCC 22019, D = *M. gypseum* NCPF580, E = *T. mentagrophytes var. erinacei* NCPF375, F = *T. tonsurans* NCPF245

3 CONCLUSION

In the present study, in an attempt to discover novel antibacterial and antifungal agents, 12 diverse derivatives of thiosemicarbazide, 4-thiazolidinone and 1,2,4-triazole-3-thione were designed and synthesized. Structural elucidation of the synthesized compounds was performed and verified by IR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry and elemental analysis.

The compounds were screened for their antibacterial and antifungal activity against diverse microorganisms. Moreover, the structure activity relationships of the title compounds were examined and evaluated.

As a summary, **6d**, **7c** and **7d** were determined as the most active antibacterial compounds. Generally, 1,2,4-triazole-3-thione derivatives displayed higher antibacterial activity than thiosemicarbazide and 4-thiazolidinone derivatives. Propyl and allyl substitution of 4-position of 1,2,4 triazole-3-thione ring and 3-allyl substitution of 4-thiazolidinone ring increased the antibacterial activity of the compounds. This underlined the significance of the stated *N*-allyl substitution for antibacterial activity of 1,2,4-triazole-3-thione and 4-thiazolidinone derivatives.

Compound **6d**, which has an allyl group at the 3-position of 4-thiazolidinone ring, was also found as the most active antifungal compounds within our compounds. This indicated that 3-allyl substitution of 4-thiazolidinones is not only important for their antibacterial activity but also their antifungal activity.

The findings revealed the promising antibacterial and antifungal activity of thiosemicarbazide, 1,2,4-triazole-3-thione and 4-thiazolidinone derivatives and these derivatives could be an interesting starting point for further structural optimization to obtain novel promising and more potent antimicrobial agents.

4 EXPERIMENTAL

4.1 Chemistry

4.1.1 General

IR spectra were recorded on KBr discs, using a Shimadzu IR Affinity-1 FT-IR instrument. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Varian UNITY INOVA spectrometer in DMSO-d_6 solution. Chemical shifts (δ) were reported in ppm; coupling

constants (*J*) were recorded in hertz (Hz). Mass spectra were obtained on a VG Zab Spec (70 eV) instrument. The reactions were monitored by TLC aluminum plates with silica gel

Kieselgel 60 F_{254} thickness 0.25 mm (Merck), using UV light as a visualizing agent. All reagents and solvents were purchased from Merck, Fluka and Sigma-Aldrich and were used without further purification.

4.1.2 General procedure for the synthesis of compounds 1-4

The starting compounds **1-4** were prepared as described in the literature.[50-51]

2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetohydrazide (4)

The analytical and spectral data belonging compound **4** were described in the literature as following:[53-55]

M.p. 171-172 ^{o}C. IR υ_{max} (KBr, cm^{-1}): 3627, 3567 (N-H stretching); 1671 (C=O stretching). ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6): 9.48 (br.s., 1H, NH), 7.66 (d, J = 8.6 Hz, 2H, ar), 7.47 (d, J = 3.7Hz, 1H, C_5-H), 7.29 (d, J = 8.6 Hz, 2H, ar), 6.37 (dd, J = 3.5 ; 1.8 Hz, 1H, C_4-H), 6.23 (d, J = 3.5 Hz, 1H, C_3-H), 3.81, (s, 2H, SCH_2), 3.45 (br.s., 1H, NH_2).

4.1.3 General procedure for the synthesis of 2-(2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-(alkyl/alkenyl/aryl)hydrazinecarbothioamides (5a-f)

0.005 mol various substituted isothiocyanates were added to a solution of 0.005 mol 2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetohydrazide in 20 mL of absolute ethanol and heated in a water bath for 3 hours under reflux. After cooling, the precipitate was separated and purified either by washing with hot EtOH or recrystallization from EtOH.

2-(2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-methylhydrazinecarbothioamide (5a)

White solid, m.p. 176-177 ^{o}C, yield: 93.92%. Anal. Calcd. for $C_{16}H_{15}BrN_6O_2S_2$: C, 41.11; H, 3.23; N, 17.98 %. Found: C, 41.38; H, 3.31; N, 17.62 %. IR υ_{max} (KBr, cm^{-1}): 3280 (N-H stretching), 1705 (C=O stretching), 1542, 1513, 1491, 1450 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 10.19 (s, 1H, NH), 9.35 (s, 1H, NH), 8.22 (s, 1H, NH), 7.84 (d, J = 8.30 Hz, 2H, BrPh), 7.77 (d, J = 1.95 Hz, 1H, furan C_5-H), 7.51 (d, J = 8.30 Hz, 2H, BrPh), 6.54 (dd, J = 3.41 ; 1.95 Hz, 1H, furan C_4-H), 6.31 (d, J = 3.41 Hz, 1H, furan C_3-H), 3.89 (s, 2H, SCH_2), 2.95 (s, 3H, CH_3). ^{13}C NMR (APT) (125 MHz, δ ppm, DMSO-d_6): 182.63 (C=S), 167.08 (C=O), 151.94 (Fur C2), 147.72 (TR C5), 145.61 (Fur C5), 141.02 (TR C3), 133.60 (BrPh C3,5), 133.11 (BrPh C1), 130.35 (BrPh C2,6), 124.51 (BrPh C4), 112.26

(fur C3,4), 34.68 (CH_2), 31.47 (CH_3). EIMS [m/z (%)]: 468 [(M+2), 4], 466 (M^+, 4), 395 (6), 393 (6), 364 (16), 362 (16), 323 (100), 321 (96), 269 (27), 267 (27), 250 (18), 248 (18).

2-(2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-ethylhydrazinecarbothioamide (5b)

The analytical and spectral data belonging compound **5b** were reported in the literature.[55]

2-(2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-propylhydrazinecarbothioamide (5c)

White solid, m.p. 203-204 ^oC, yield: 83.23%. Anal. Calcd. for $C_{18}H_{19}BrN_6O_2S_2$: C, 43.63; H, 3.86; N, 16.96 %. Found: C, 43.66; H, 3.97; N, 16.74 %. IR υ_{max} (KBr, cm^{-1}): 3341 (N-H stretching), 1710 (C=O stretching), 1536, 1492, 1455, 1426 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 10.16 (s, 1H, NH), 9.27 (s, 1H, NH), 8.16 (s, 1H, NH), 7.84 (d, *J* = 8.30 Hz, 2H, BrPh), 7.78 (d, *J* = 1.96 Hz, 1H, furan C_5-H), 7.50 (d, *J* = 8.78 Hz, 2H, BrPh), 6.54 (dd, *J* = 3.42, 1.95 Hz, 1H, furan C_4-H), 6.31 (d, *J* = 3.41 Hz, 1H, furan C_3-H), 3.88 (s, 2H, SCH_2), 3.45 (q, *J* = 6.83 Hz, 2H, N-CH_2), 1.55 (sx, *J* = 6.83 Hz, 2H, CH_2), 0.81 (t, *J* = 7.32 Hz, 3H, CH_3).

2-(2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-allylhydrazinecarbothioamide (5d)

The analytical and spectral data belonging compound **5d** were reported in the literature.[55]

2-(2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-phenylhydrazinecarbothioamide (5e)

The analytical and spectral data belonging compound **5e** were reported in the literature.[55]

2-(2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-(4-methylphenyl)hydrazinecarbothioamide (5f)

White solid, m.p. 185-186 ^oC, yield: 99.50%. Anal. Calcd. for $C_{22}H_{19}BrN_6O_2S_2$: C, 48.62; H, 3.52; N, 15.46 %. Found: C, 48.42; H, 3.33; N, 15.19 %. IR υ_{max} (KBr, cm^{-1}): 3199 (N-H stretching), 1688 (C=O stretching), 1593, 1514, 1490, 1424 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 10.30 (s, 1H, NH), 9.64 (s, 1H, NH), 9.60 (s, 1H, NH), 7.83; 7.80 (d, *J* = 8.30 ; 8.79 Hz, 2H, BrPh), 7.77 (d, *J* = 0.98 Hz, 1H, furan C_5-H), 7.51-7.11 (m, 6H, ar.), 6.54 (dd, *J* = 3.91 ; 1.46 Hz, 1H, furan C_4-H), 6.31 (d, *J* = 3.41 Hz, 1H, furan, C_3-H), 4.09 ; 3.95 (2s, 2H, SCH_2), 2.35 ; 2.27 (2s, 3H, CH_3).

4.1.4 General procedure for the synthesis of 2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*'-(3-(alkyl/alkenyl/aryl)-4-oxothiazolidin-2-ylidene)acetohydrazides (6a-e)

A mixture of 0.005 mol 2-(2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-(alkly/aryl)hydrazinecarbothioamide, 0.005 mol of ethyl bromoacetate, and 0.02 mol of fused sodium acetate in 25 mL anhydrous EtOH is heated under reflux for 3 hours. The reaction mixture is cooled, diluted with water, and allowed to stand overnight. The precipitate was filtered, dried, and recrystallized from EtOH.

2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*'-(3-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6a)

White solid, m.p. 222-223 ^{o}C, yield: 81.74%. Anal. Calcd. for $C_{18}H_{15}BrN_6O_3S_2$: C, 42.61; H, 2.97; N, 16.56 %. Found: C, 42.84; H, 3.17; N, 16.73 %. IR υ_{max} (KBr, cm^{-1}): 3232 (N-H stretching), 1720 (C=O ring, stretching), 1645 (C=O stretching), 1592, 1509, 1491, 1446 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 10.54 (s, 1H, NH), 7.81 (d, *J* = 8.79 Hz, 2H, BrPh), 7.76 (d, *J* = 0.97 Hz, 1H, furan C_5-H), 7.48 (d, *J* = 8.30 Hz, 2H, BrPh), 6.53 (dd, *J* = 3.42 ; 1.96 Hz, 1H, furan C_4-H), 6.31 (d, *J* = 3.41 Hz, 1H, furan C_3-H), 4.02 ; 4.01 (2s, 4H, SCH_2), 3.06 (s, 3H, NCH_3). ^{13}C NMR (APT) (125 MHz, δ ppm, DMSO-d_6): 171.76 (ring C=O), 163.60 (C=O), 158.31 (C=N), 151.51 (Fur C2), 147.66 (TR C5), 145.49 (Fur C5), 141.24 (TR C3), 133.48 (BrPh C3,5), 133.11 (BrPh C1), 130.40 (BrPh C2,6), 124.31 (BrPh C4), 112.22; 112.05 (fur C3,4), 35.44 (ring CH_2), 33.44 (CH_2), 29.62 (CH_3). EIMS [m/z (%)]: 508 [(M+2), 29], 506 (M^+, 26), 364 (98), 362 (100), 323 (27), 321 (26), 269 (8), 267 (7), 250 (12), 248 (12).

2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*'-(3-ethyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6b)

White solid, m.p. 164-165 ^{o}C, yield: 97.14%. Anal. Calcd. for $C_{19}H_{17}BrN_6O_3S_2$: C, 43.76; H, 3.28; N, 16.11 %. Found: C, 44.48; H, 3.96; 15.45 %. IR υ_{max} (KBr, cm^{-1}): 3473 (N-H stretching), 1716 (C=O ring, stretching), 1684 (C=O stretching), 1603, 1513, 1493, 1456 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 10.54 (s, 1H, NH), 7.82 (d, *J* =8.30 Hz, 2H, BrPh), 7.76 (d, *J* = 0.98 Hz, 1H, furan C_5-H), 7.49 (d, *J* = 8.79 Hz, 2H, BrPh), 6.53 (dd, *J* =3.42 ; 1.95 Hz, 1H, furan C_4-H), 6.31 (d, *J* = 2.93 Hz, 1H, furan C_3-H), 4.02 ; 4.01 (2s, 4H, SCH_2), 3.65 ; 3.45 (2q, *J* = 7.32 Hz, 2H, N-CH_2), 1.11 ; 1.06 (2t, *J* = 7.32 Hz, 3H, CH_3).

2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*'-(3-propyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6c)

White solid, m.p. 171-172 ^{o}C, yield: 88.11%. Anal. Calcd. for $C_{20}H_{19}BrN_6O_3S_2$: C, 44.86; H, 3.57; N, 15.69 %. Found: C, 45.10; H, 4.09; N, 15.32 %. IR υ_{max} (KBr, cm^{-1}): 3473 (N-H stretching), 1716 (C=O ring, stretching), 1683 (C=O stretching), 1601, 1513, 1492, 1457 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 10.54 (s, 1H, NH), 7.80 (d, *J* = 8.78 Hz, 2H, BrPh), 7.76 (d, *J* = 1.47 Hz, 1H, furan C_5-H), 7.48 (d, *J* = 8.78 Hz, 2H, BrPh), 6.53 (dd, *J* = 3.42 ; 1.96 Hz, 1H, furan C_4-H), 6.31 (d, *J* = 3.41 Hz, 1H, furan C_3-H), 4.04; 4.00 (2s, 4H, SCH_2), 3.58; 3.43 (2t, *J* = 7.32 Hz, 2H, N-CH_2), 1.60-1.56 (m, 2H, CH_2), 1.04 ; 0.83 (2t, *J* = 7.32 Hz, 3H, CH_3).

2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*'-(3-allyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6d)

White solid, m.p. 174-175 ^{o}C, yield: 88.23%. Anal. Calcd. for $C_{20}H_{17}BrN_6O_3S_2$: C, 45.03; H, 3.21; N, 15.75 %. Found: C, 44.95; H, 3.84; N, 15.98 %. IR υ_{max} (KBr, cm^{-1}): 3473 (N-H stretching), 1718 (C=O ring, stretching), 1670 (C=O stretching), 1602, 1512, 1492, 1424 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 10.56 (s, 1H, NH), 7.81 (d, *J* = 8.30 Hz, 2H, BrPh), 7.76 (d, J = 1.95 Hz, 1H, furan C_5-H), 7.48 (d, *J* = 8.79 Hz, 2H, BrPh), 6.53 (dd, *J* = 3.41 ; 1.96 Hz, 1H, furan C_4-H), 6.31 (d, *J* = 3.42 Hz, 1H, furan C_3-H), 5.83-5.76 (m, 1H, CH=), 5.18 (d, *J* = 17.57 Hz, 1H, =CH_2 trans), 5.14 (d, *J* = 9.76 Hz, 1H, =CH_2 cis), 4.22 (d, *J* = 5.37 Hz, 2H, N-CH_2), 4.06 ; 4.00 (2s, 4H, SCH_2).

2-((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*'-(3-phenyl-4-oxothiazolidin-2-ylidene)acetohydrazide (6e)

White solid, m.p. 222-223 ^{o}C, yield: 82.35%. Anal. Calcd. for $C_{23}H_{17}BrN_6O_3S_2$: C, 48.51; H, 3.00; N, 14.75 %. Found: C, 47.84; H, 2.82; N, 14.83 %. IR υ_{max} (KBr, cm^{-1}): 3473 (N-H stretching), 1727 (C=O ring stretching), 1670 (C=O stretching), 1569, 1512, 1490, 1443 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 10.49 (s, 1H, NH), 7.78 (d, *J* = 8.30 Hz, 2H, BrPh), 7.75 (d, *J* = 1.95 Hz, 1H, furan, C_5-H), 7.50-7.29 (m, 7H, ar), 6.53 (dd, *J* = 3.42 ; 1.96 Hz, 1H, furan C_4-H), 6.29 (d, *J* = 3.42 Hz, 1H, furan C_3-H), 4.17 ; 3.95 (2s, 4H, SCH_2).

4.1.5 General procedure for the synthesis of 5-(((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-4-(alkyl/alkenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (7a-d)

A solution of 0.005 mol 2-(2-((4-(4-bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetyl)-*N*-(alkly/aryl)hydrazinecarbothioamide in 2N aqueous NaOH (20 mL) was heated under reflux for 2h. After cooling, the reaction mixture was acidified by the addition of 12.5% aqueous HCI. The precipitate thus obtained was collected by filtration, washed with water several times and purified by recrystallization from EtOH.

5-(((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-4-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (7a)

White solid, m.p. 218-220 ^{o}C, yield: 75.70%. Anal. Calcd. for $C_{16}H_{13}BrN_6OS_2$: C, 42.76; H, 2.91; N, 18.70 %. Found: C, 42.62; H, 2.96; N, 18.19 %. IR υ_{max} (KBr, cm^{-1}): 3420 (N-H stretching), 1570, 1491, 1451, 1400 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 13.59 (s, 1H, NH), 7.80 (d, *J* = 8.79 Hz, 2H, BrPh), 7.78 (d, *J* = 1.95, 1H, furan C_5-H), 7.41 ; 7.36 (2d, *J* = 8.78 Hz, 2H, BrPh), 6.53 (dd, *J* = 3.42 ; 1.95 Hz, 1H, furan C_4-H), 6.32 ; 6.11 (2d, *J* = 3.41 ; 4.39 Hz, 1H, furan C_3-H), 4.35 (s, 2H, SCH_2), 3.45 (s, 3H, NCH_3). ^{13}C NMR (APT) (125 MHz, δ ppm, DMSO-d_6): 168.84; 167.82 (C=S), 149.46; 149.12 (Fur C2), 148.06 (FurTR C5), 145.92; 145.69 (Fur C5), 143.39 (TR C5), 141.13; 140.15 (TR C3), 134.13 (BrPh C1), 133.43; 133.11 (BrPh C3,5), 131.46; 130.22 (BrPh C2,6), 124.29; 123.79 (BrPh C4), 113.21; 112.28 (fur C3,4), 30.51 (CH_3), 27.99 (CH_2). EIMS [m/z (%)]: 450 [(M+2), 10], 448 (M^+, 8), 323 (99), 321 (100), 269 (25), 267 (26), 250 (6), 248 (5).

5-(((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-4-ethyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (7b)

White solid, m.p. 258-259 ^{o}C, yield: 93.28%. Anal. Calcd. for $C_{17}H_{15}BrN_6OS_2$: C, 44.06; H, 3.26; N, 18.13 %. Found: C, 44.59; H, 2.98; N, 17.61 %. IR υ_{max} (KBr, cm^{-1}): 3439 (N-H stretching), 1569, 1491, 1450, 1400 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 13.58 (s, 1H, NH), 7.80 (d, *J* = 8.78 Hz, 2H, BrPh), 7.78 (d, *J* = 1.96 Hz, 1H, furan C_5-H), 7.42 (d, *J* = 8.79 Hz, 2H, BrPh), 6.52 (dd, *J* = 3.41 ; 1.96 Hz, 1H, furan C_4-H), 6.11 (d, *J* = 3.42 Hz, 1H, furan C_3-H), 4.35 (s, 2H, SCH_2), 3.92 (q, *J* = 7.32 Hz, 2H, N-CH_2), 1.14 ; 1.06 (2t, *J* = 7.32 Hz, 3H, CH_3).

5-(((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-4-propyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (7c)

White solid, m.p. 263-264 ^{o}C, yield: 92.78%. Anal. Calcd. for $C_{18}H_{17}BrN_6OS_2$: C, 45.28; H, 3.59; N, 17.60 %. Found: C, 44.99; H, 2.88; N, 17.11 %. IR υ_{max} (KBr, cm^{-1}): 3447 (N-H stretching), 1526, 1492, 1457, 1402 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 13.59 (s, 1H, NH), 7.79 (d, *J* = 8.79 Hz, 2H, BrPh), 7.77 (d, *J* = 1.95 Hz, 1H, furan C_5-H), 7.42 (d, J = 8.29 Hz, 2H, BrPh), 6.52 (dd, *J* = 3.42 ; 1.95 Hz, 1H, furan C_4-H), 6.11 (d, *J* = 3.42 Hz, 1H, C_3-H), 4.36 (s, 2H, SCH_2), 3.43 (t, *J* = 6.83 Hz, 2H, N-CH_2), 1.73-1.47 (m, 2H, $C\underline{H_2}CH_3$), 1.04 (t, *J* = 6.84 Hz, 3H, CH_3).

5-(((4-(4-Bromophenyl)-5-(furan-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-4-allyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (7d)

White solid, m.p. 249-250 ^{o}C, yield: 98.75%. Anal. Calcd. for $C_{18}H_{15}BrN_6OS_2$: C, 45.47; H, 3.18; N, 17.67 %. Found: C, 44.93; H, 3.05; N, 17.56 %. IR υ_{max} (KBr, cm^{-1}): 3422 (N-H stretching), 1570, 1491, 1449,1400 (C=N, C=C stretching). ^{1}H-NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 13.69 (s, 1H, NH), 7.80 (d, *J* = 8.30 Hz, 2H, BrPh), 7.78 (d, *J* = 1.96 Hz, 1H, furan C_5-H), 7.42 (d, *J* = 8.78 Hz, 2H, BrPh), 6.52 (dd, *J* = 3.42 Hz ; 1.95 Hz, 1H, furan C_4-H), 6.11 (d, *J* = 2.93 Hz, 1H, furan C_3-H), 5.90-5.60 (m, 1H, CH=), 5.15 (d, *J* = 9.28 Hz, 1H, = CH_2 cis), 5.02 (d, *J* = 18.54 Hz, 1H, = CH_2 trans), 4.62 (d, *J* = 5.37 Hz, 2H, N-CH_2), 4.33 (s, 2H, SCH_2).

4.2 Biological activity assays

The stock solutions of the title compounds were prepared by dissolving them in dimethyl sulfoxide with a density of 3200 µg/mL. RPMI 1640 medium was utilized to obtain the final concentration for *Candida* species as well as the dermatophytes. Besides, Mueller-Hinton broth was utilized for obtaining the aimed concentration of the tested bacterias. In the end, the concentrations of the samples were diminished to 1%.

4.2.1 Antibacterial activity

Microbroth dilution method was utilized to detect the minimum inhibitory concentrations. National Committee for Clinical Laboratory Standards (NCCLS) recommendations were followed while performing the microbroth dilution method.[56] Mueller-Hinton broth was

utilized as the test analysis medium. Inoculums with an amount of 5 x 10^5 CFU cm^{-3} were applied for each well. The dilutions of the title compounds, whose concentrations were diminished for two times (64-0.25 µg/mL), were prepared. Besides, additional dilutions were applied for antibiotic standards (0.12-0.015 µg/mL). The incubation process of the plates was performed in an ambient air incubator. The incubation process was conducted for 16-20h at 95 ^oF temperature. The minimum concentration of the analyzed compounds that inhibits visible growth was stated as the minimum inhibitory concentration value.

4.2.2 Antifungal activity

4.2.2.1 Antifungal activity for *Candida* species

Microbroth dilution method was utilized to detect the minimum inhibitory concentrations. National Committee for Clinical Laboratory Standards (NCCLS) recommendations were followed while performing the microbroth dilution method.[57] RPMI 1640 was utilized to obtain RPMI broth. For this, 0.3-gram glutamine was added for each liter of RPM 1640. Then buffering was applied with 3-(*N*-morpholino)-propanesulfonic acid (MOPS), and the pH was set as 7.0. Afterward, the inoculum suspension was set by 1% dilution of 0.5 McFarland standards yeast solution in 0.85% saline followed by 0.05 dilution in RPMI broth.

Title dilutions of the title compounds were prepared from 64 to 0.25 µg/mL with the suspension of the inoculum. Superior dilutions were applied for the standard compound, itraconazole (0.12-0.015 µg/mL). The incubation process of the plates was performed in an ambient air incubator. The incubation process was conducted for 48h at a temperature of 95 ^oF. The minimum concentration of the analyzed compounds that inhibits visible growth, was defined as the minimum inhibitory concentration value.

4.2.2.2 Antifungal activity for dermatophytes

The Microdilution method was utilized by following the classical protocol of NCCLS.[56] L-glutamine and RPMI 1640 were buffered with 3-(*N*-morpholino)-propanesulfonic acid. Then, the pH of the medium was set as 7.0 at a temperature of 77 ^oF. The process for the preparation of the suspensions of the inoculums was conducted by following the NCCLS guidelines[58] and previously reported procedure.[59]

The separations were cultured on potato dextrose agar plates at 82.4 ^oF for two weeks. Then, 1 cm^{-3} of 0.85% saline were added to obtain a suspension of the fungal colonies. The obtained

suspension was transferred to a sterile tube. The massive compounds were let to settle for 20 minutes at 69.8 ^{o}F. Then the upper suspension was mixed for 15 seconds by utilizing a vortex. The composed turbidness of supernatants was analyzed spectrophotometrically at 530 nm wavelength. The obtained suspensions were diluted 2% in RPMI to get the end sizes of inoculum (from 0.4 x 10^4 to 5 x 10^4 CFU cm^{-3}). After the preparation of the microdilution plates, they were frozen at -94 ^{o}F until the usage time. Rows from 2 to 12 included a diverse series of drug solutions in 100 µL volumes and 1st row included 100 µL drug-free medium, which was used as growth control. The inoculations were performed for each well on the day of the analysis with 100 µL volumes of the corresponding inoculum. By this step, the final analysis concentrations were obtained. The incubation process was performed for the microplates for 1 week at a temperature of 82.4 ^{o}F. At the end of 1 week, the microplates were evaluated visually with the help of an inverted reading mirror for dermatophytes. For all compounds, minimum inhibitory concentration was defined as the minimal concentration displaying 100% inhibition of growth.

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CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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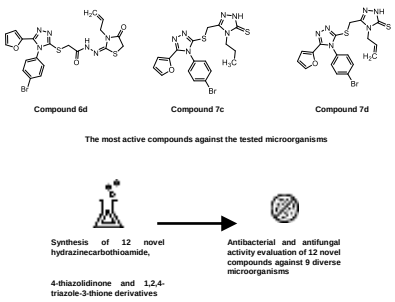
Entry for the Table of Contents

Graphic for Table of Contents



Text for Table of Contents

A series of novel hydrazinecarbothioamide, 4-thiazolidinone and 1,2,4-triazole-3-thione derivatives were synthesized and assayed for their antibacterial and antifungal activities against 9 diverse microorganisms (*S. aureus* (ATCC 29213), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC27853), *C. albicans* (ATCC10231), *C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019), *M. gypseum* (NCPF580), *T. metagrophytes var. erinacei* (NCPF 375) and *T. tonsurans* (NCPF 245). Some compounds displayed remarkable antibacterial and

antifungal activity against the tested microorganisms. Particularly, 4-propyl and allyl substitution of 1,2,4-triazole-3-thiones and 3-allyl substitution of 4-thiazolidinones increased the antimicrobial activities.