Synthesis and Antimicrobial Activity of New 1, 2, 4-Triazole, 1, 3, 4-Oxadiazole, 1, 3, 4-Thiadiazole, Thiopyrane, Thiazolidinone and Azepine Derivatives

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ABSTRACT: 4-oxo-4-phenylbutanehydrazide **3** was reacted with aryl or alkyl isothiocyanates to give the corresponding *N*-substituted-2-(4-oxo-4-phenylbutanoyl) hydrazine-1-carbothioamide **4a-c**. Cyclization of thiosemicarbazides **4a-c** with sodium hydroxide led to the formation of 3-(4-sub-5-thioxo-1, 2, 4-triazol-3-yl)-propanone **5a-c**. Desulfurization of thiosemicarbazides **4a-c** by mercuric oxide afforded 3-(5-(sub-amino)-1, 3, 4-oxadiazol-2-yl)-propanone **6a-c**. The reaction of **4a-c** with phosphorus oxychloride gave 3-(5-(sub-amino)-1, 3, 4-thiadiazol-2-yl)-propanone **7a-c**. Treatment of **4a-c** with ethylbromoacetate or α-bromopropionic acid gave *N'*-(3-sub-thiazolidin-2-ylidene)-butanehydrazide **8a-c** and (*N'*-(3-sub-oxothiazolidin-2-ylidene)-butanehydrazide **9a-c**. Chlorination of oxothiazolidine-hydrazide **9a-c** by phosphorus oxychloride afforded *N*-(3-sub-4-oxothiazolidine)-butane-hydrazonoyl-chloride **10a-c**. The reaction of **10a-c** with mercaptoacetyl-chloride yielded 2-((4-benzoyl-thiopyrane) hydrazono)-3-sub-thiazolidinone **11a-c**. Also, reacted of **10a-c** with hydrazine hydrate afforded *N''*-(3-sub-oxothiazolidine)-butane-hydrazon-hydrazide **12a-c**. The 3-sub-2-((pyridazine) hydrazono) thiazolidinone **13a-c** was obtained by cyclization of **12a-c** *via* refluxing in DMF. The reaction and cyclized of **9a-c** with chloroacetyl-chloride in ethanolic KOH afforded 1-((3-sub-4-oxothiazolidine) amino)-azepine-dione **14a-c**. The chemical structures of the new compounds have been confirmed by diverse spectroscopy analyses such as IR, NMR, MS and elemental analysis. The synthesized compounds were tested for their antimicrobial activity and these compounds were considered (Pyridazin-hydrazono-thiazolidinone **13a-c**, oxothiazolidin-azepinedione **14a-c**, *N*-thiazolidin-hydrazonhydrazide **12a-c** and thiopyran-hydrazono-thiazolidinone **11a-c**) the most effective as antimicrobial activity.

Keywords: 1, 2, 4-triazole, 1, 3, 4-oxadiazole, 1, 3, 4-thiadiazole, oxothiazolidine, hydrazide, thiopyranone, pyridazine, azepine, isothiocyanates, thiosemicarbazides, antimicrobial activity.

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1. INTRODUCTION

A wide diversity of pharmacological characteristic is associated with many heterocyclic compounds such as; 1, 2, 4-Triazole derivatives are known to their biological activity as antimicrobial, [1-3] Analgesic, anticonvulsant and anti-inflammatory, [4] anti-tumor, [5] antiviral, [6] and anti-parasitic. [7] Also, 1, 3, 4-oxadiazoles have been famous for eighty years, thus it have important biological activities such as anti-spasmolytic and hypotensive, [8] anticonvulsant, [9] antimicrobial, [10] anti-inflammatory and analgesic, [11] anticancer, [12] anti-proliferative, [13] anti-allergic, [14] and hypoglycemic, [15]. Moreover, the interaction of 1, 3, 4-oxadiazole or 1, 3, 4-thiadiazole derivatives with CT-DNA was investigated by different spectroscopic methods, [16-17] hence can benefit in understanding the binding mechanism of heterocyclic molecules and the design of new effective molecules. Also, the interaction of DNA with 1,3,4-oxadiazoles or 1, 3, 4-thiadiazoles lead to the formation of anti-proliferative cells, anticancer and antitumor agents through many scientific studies, [18-20] thus these compounds have the ability to the binding to DNA which makes researchers use these compounds to develop many drugs in the future.

Furthermore, the 1, 3, 4-thiadiazole moiety is one of the most significant and well-known heterocycles, which is a widespread and complement advantage of an assortment of natural products and pharmaceutical, thiadiazole ring is existent as a core component in an organized of drug categories. So, the 1, 3, 4-thiadiazole ring has become an important structure for the development of new drugs because the 1, 3, 4-thiadiazole derivatives have a broad biological activities spectrum such as antimicrobial, [21] anticancer, [22] anticonvulsant, [23] anti-inflammatory and analgesic, [24] antiviral, [25] anti-leishmanial, [26] trypanocidal activity (anti-epimastigote), [27] and carbonic anhydrase inhibitory activity. [28] Moreover, Thiazolidinone ring systems are known to possess many pharmacological activities including antioxidant, [29] antiviral, [30] antibacterial, [31] antituberculosis, [32] and pyrazolo-oxothiazolidines as anti-proliferative agents against human lung cancer cell line A549, [33] the 2-(acetyloxy)-*N*-(5-nitro-2-thiazolyl) benz-amide formally known as *Nitazoxanide* (NTZ) drug (Fig.1) is an antiprotozoal drug. [34] Besides, Azepines (seven-member ring) is considering heterocyclic compounds containing a nitrogen atom and used to treat many diseases as the anticancer and tumor metastasis inhibitory activities, [35, 36] antimicrobial, [3] and carbamazepine is used anti-depressants with anticonvulsant and analgesic properties, [37] and mirtazapine is used as an antiemetic in animals, but in humans, it too has antihistaminic,

insomnia, sedative, antidepressant and anxiolytic activity. [38] Also, diverse pharmacologically valuable alkaloids have been specified which displayed a broad range of biological activities including anticancer, antimalarial, and antiarrhythmic properties, members of the rhazinilam - leuconoxine - mersicarpine triad of alkaloids occur in the plant family *Apocynaceae*, recently, these natural products have been found in the following genera: *Leuconotis, Alstonia, Aspidosperma*, [39] shown in (**Figure 1**).

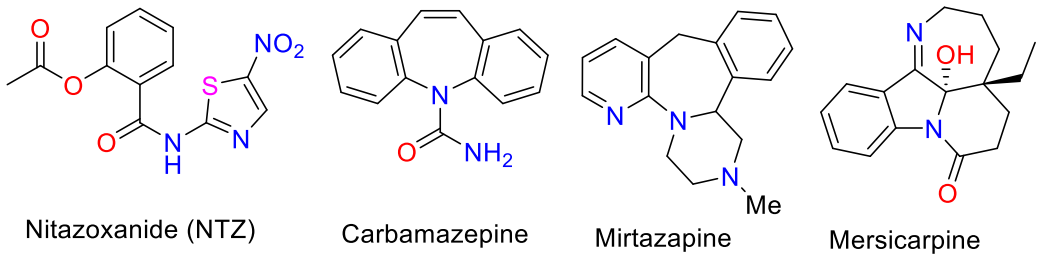


Fig.1. Chemical structure of many pharmaceutical activities

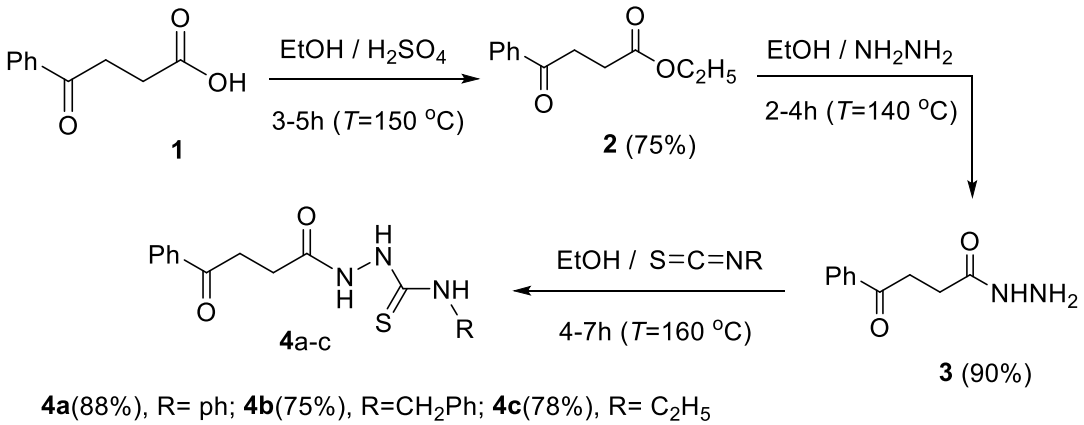
Moreover, the pyridazine derivatives have diverse types of biological activity such as anti-inflammatory and analgesic activity, [40] antimicrobial, [41] anti-tubercular, [42] and anti-secretory, anti-ulcer, antihistamine. [43] Also, more scientific researches have been published in the field of medicinal chemistry containing heterocyclic compounds that possess multiple biological and pharmaceutical activities. [44-50] In continuation of our research work in this manuscript, we prepared new heterocyclic compounds such as *N*- hydrazine-carbothioamides; 1, 2, 4-triazoles; 1, 3, 4-oxadiazoles; 1, 3, 4-thiadiazoles; 4-oxothiazolidines; pyridazin-hydrazono-thiazolidinones; oxothiazolidin-azepine-diones with studying their activities as antimicrobial.

2. RESULTS AND DISCUSSION

2.1. Chemistry

Treatment of 3-benzoylpropionic acid (**1**) with absolute ethanol containing 3-4 drops of concentrated H_2SO_4 gave ethyl 4-oxo-4-phenylbutanoate (**2**). [41] However, refluxing (**2**) with hydrazine hydrate for 3-5 hours led to the formation of 4-oxo-4-phenylbutanehydrazide (**3**), the IR spectrum of **3** displayed the absence of an ester group and revealed absorption bands at *v* 3405-3325 cm^{-1} due to the NH-NH_2 group and 1722 and 1675 cm^{-1} for the two ketone and amide

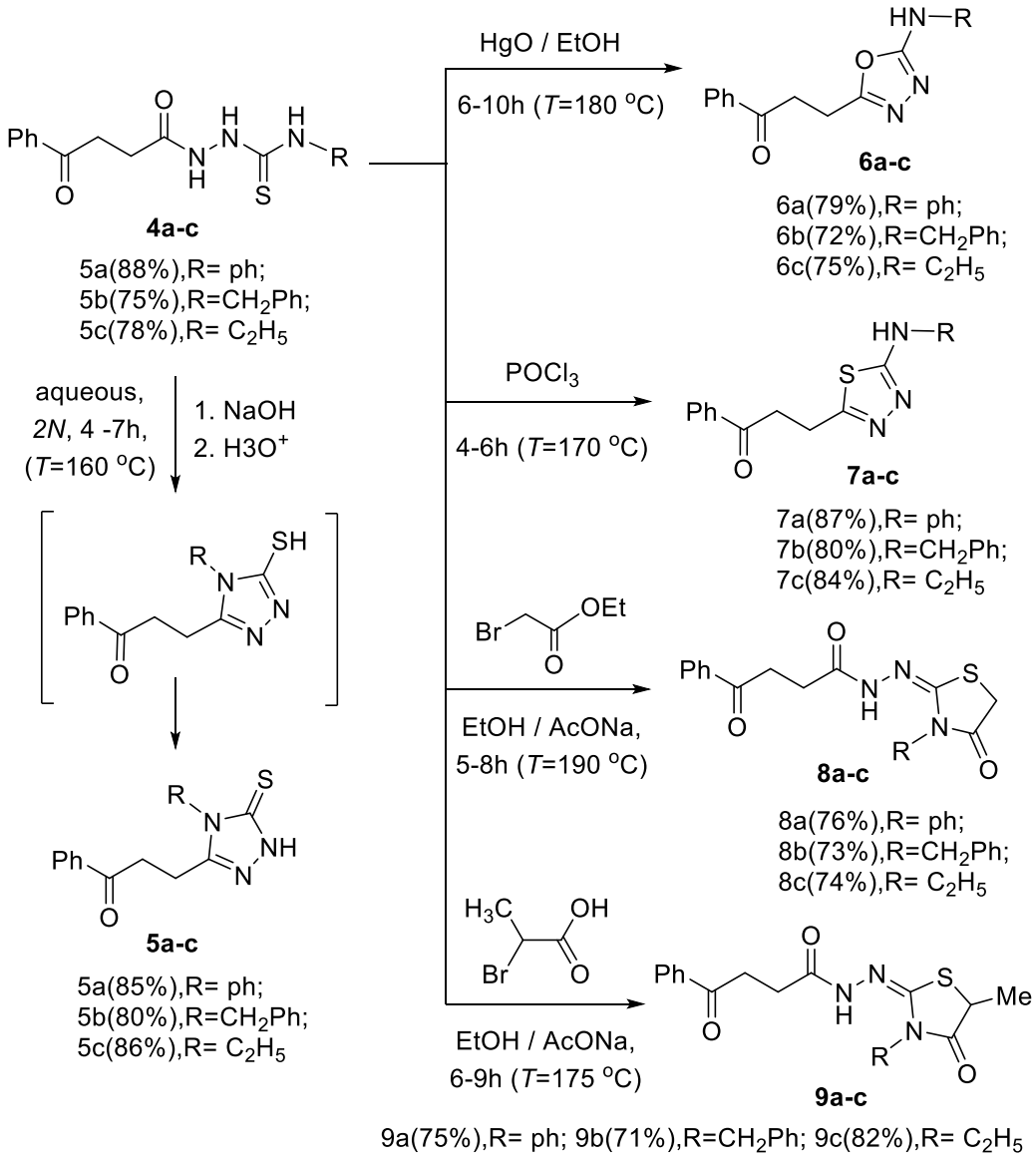
carbonyl groups. The ^{1}H-NMR spectrum of **3** showed two singlet signals at δ 6.10, 9.08 ppm corresponding to the two and one protons of the (NH_2) and (NH) groups (with D_2O exchangeable), respectively. Moreover, compounds **3** was reacted with isothiocyanate derivatives, [20] namely phenyl-, benzyl-, and ethylisothiocyanate, to afford *N*-substituted-2-(4-oxo-4-phenylbutanoyl) hydrazine-1-carbothioamide (**4a-c**) in good yields. The chemical structures of **4a-c** were allocated on the basis of their spectral data and elemental analyses. IR spectrum exhibited absorption bands at v 3330-3155 cm^{-1} (3NH), 1725-1718 and 1684-1680 cm^{-1} (2CO), and the vibration coupling due to N-C=S functions at 1357-1350 cm^{-1}. ^{1}H-NMR spectrum of **4a** evidenced three singlet broad signals at δ 9.90, 10.70, 11.60 ppm conforming to the three protons of the (3NH) group (with D_2O exchangeable). The MS of **2, 3, 4a, 4b** and **4c** exposed molecular ion peaks at *m/z* = 206 (M^+, 100%), 192 (M^+, 100%), 327 (M^+, 100%), 341 (M^+, 90%), 279 (M^+, 95%), respectively. All spectral data (IR, NMR, and Mass) and elemental analysis of new compounds were clarified in the experimental section (**Scheme 1**).



Scheme 1: Synthesis of *N*-substituted-hydrazine-1-carbothioamide (**4a-c**) derivatives

Cyclization of *N*-substituted-2-(4-oxo-4-phenylbutanoyl) hydrazine-1-carbothioamide (**4a-c**) *via* refluxing and heating with aqueous sodium hydroxide, [20] to give the 3-(4-substituted -5-thioxo-4, 5-dihydro-1*H*-1, 2, 4-triazol-3-yl)-1-phenylpropan-1-one (**5a-c**), all spectral data of compounds **5a-c** were agreed with the suggested structures. The IR spectrum of compound **5a-c** designated the existence of broad band absorption at v 3315-3305 cm^{-1} of one NH group, 1722-1715 cm^{-1} of the one carbonyl group and a stretching band in the zone of 1621-1617 cm^{-1}, special to the C=N of triazole ring.^{1}H-NMR of **5a** showed one singlet broad signal at δ 12.10 ppm to the one proton of the (NH) group (with D_2O exchangeable). Also, Desulfurization of

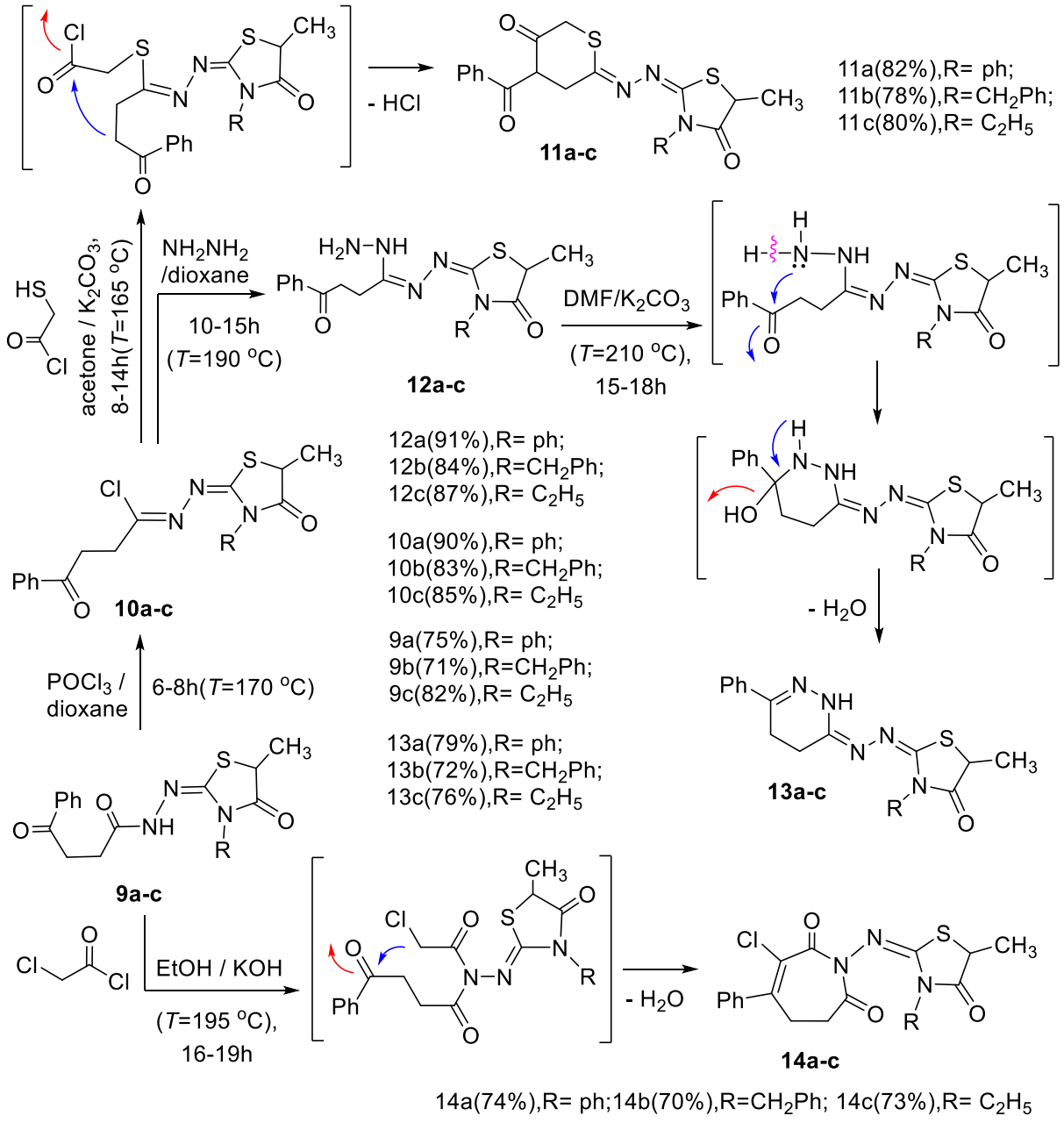
thiosemicarbazides (**4a-c**) through yellow mercuric oxide in refluxing and boiling ethanol, [20] afforded 3-(5-(substituted-amino)-1, 3, 4-oxadiazol-2-yl)-1-phenylpropan-1-one (**6a-c**) in good yields. The structures of **6a-c** were confirmed on the foundation of elemental analyses, IR, NMR, and mass spectra. The IR spectra of **6a-c** shown the presence of a broad band absorption at *v* 3265-3255 cm^{-1} of one NH group, 1726-1723 cm^{-1} of the one carbonyl group and a vibrational band in the region of 1623-1619 cm^{-1} for the C=N of oxadiazole ring. The mass spectrum of **6a**, **6b** and **6c** showed a molecular ion peaks at *m/z* = 293 (M^+, 98%), 307 (M^+, 90%), 245 (M^+, 95%). Meanwhile, the treatment of thiosemicarbazides **(4a-c)** with phosphorus oxychloride, [20] lead to the formation of 3-(5-(substituted-amino)-1, 3, 4-thiadiazol-2-yl)-1-phenylpropan-1-one (**7a-c**). The ^{1}H-NMR spectrums of **7a** showed two triplet signals at 2.83 and 2.93 ppm, *J* = 5.55 Hz corresponding to the four protons of the ($2CH_2$) and one singlet signals at 10.70 ppm conforming to the one proton of the (NH) groups (with D_2O exchangeable) and the ^{13}C-NMR spectrum of **7a** exposed absorption signals at δ 27.6 and 37.8ppm, conforming to two carbon atom of the ($2CH_2$) groups, and 121.9, 124.3, 127.9, 128.5, 129.8, 132.5, 136.4, 138.2, 155.1 and 161.48 ppm due to fourteen sp^2 carbons atom of the aromatic carbons, and 183.8 ppm corresponding to the one carbonyl group. Furthermore, Treatment of thiosemicarbazides (**4a-c**) with ethyl-bromoacetate, [20] afforded the *N′*-(3-substituted-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutanehydrazide (**8a-c**), The IR spectra of **8a-c** showed the absorption bands at *v* 3325-3315 cm^{-1} of one NH group, 1733, 1693 and 1685 cm^{-1} characteristic for the three carbonyl groups, and ^{1}H-NMR spectrum of **8a** evidenced one singlet signal at δ 4.25 ppm conforming to the two protons of the (CH_2) of thiazole ring and one singlet broad signal at δ 10.90 ppm agreeing to the one proton of the (NH) group (with D_2O exchangeable). The MS of **8a**, **8b** and **8c** discovered molecular ion peaks at *m/z* 367 (M^+, 100%), 381 (M^+, 92%), 319 (M^+, 96%), respectively. Nonetheless, treatment of thiosemicarbazides (**4a-c**) with α-bromopropionic acid, [20] produced (*N′*-(3-substituted-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazide (**9a-c**). The structures of **9a-c** were ascertained through spectral data and elemental analyses. ^{1}H-NMR spectrum of **9a** clearly showed a doublet signals at δ 1.77 ppm, *J* = 5.80 Hz corresponding to thee protons of the methyl group and a quartet signals at δ 4.50 ppm, *J* = 5.77 Hz conforming to the methine proton of thiazolidinone ring and a broad singlet signal at 10.71 ppm to one proton of NH group (with D_2O exchangeable). The mass spectra of **9a, 9b** and **9c** displayed molecular ion peaks at *m/z* 381 (M^+, 100%), 395 (M^+, 88%), 333 (M^+, 94%) respectively, shown in (**Scheme 2**).



Scheme 2: Synthesis of 1, 2, 4-triazoles; 1, 3, 4-oxadiazoles; 1, 3, 4-thiadiazoles; thiazolidinones

Also, *N*-(3-substituted-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutanehydrazonoyl chloride (**10a-c**) was prepared *via* gentle heating and refluxing of **9a-c** with phosphorus oxychloride in dry dioxane. The IR spectrum of **10a-c** displayed the absence of any absorption bands in the (NH) and C=O groups area. The ^{13}C-NMR spectrum of **10a** showed absorption signals at δ 24.5, 31.6, 33.9 and 57.2 ppm, conforming to four carbon atoms of the (CH_3, $2CH_2$ and CH-thiazole) groups respectively, and 127.8, 128.5, 128.8, 129.2, 132.7, 135.9, 136.6, 152.3 and 155.5 ppm due to fourteen sp^2 carbons atom of the aromatic carbons and 172.3, 185.1 ppm agreeing to the two carbonyl groups. As well, reaction of compounds (**10a-c)** with mercapto-

acetyl chloride, [46] gave the 2-((4-benzoyl-5-oxotetrahydro-2*H*-thiopyran-2-ylidene) hydrazono)-3-substituted-5-methylthiazolidin-4-one **(11a-c).** Its IR spectrum of **11a** revealed absorption bands around at *v* 1724, 1718 and 1682 cm^{-1} for three carbonyl groups and 1626 cm^{-1} for (C=N) and the ^{1}H-NMR spectrum of **11a** displayed a doublet signals at δ 1.75 ppm, J = 5.90 Hz agreeing to thee protons of the methyl group and three a doublet signals at δ 2.70, 4.02 and 4.10 ppm, J = 5.94 Hz conforming to the four protons of ($2CH_2$) thiopyran ring and a quartet signals at 4.40 ppm to one proton of CH- thiazole ring and a triplet signals at 5.95 ppm to one proton of CH-thiopyran ring. Moreover, refluxing a mixture of **10a-c** and hydrazine hydrate afforded *N''*-(3-substituted-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutanehydrazon-hydrazide **(12a-c)**. The IR spectrum of **12a-c** exhibited absorption bands around at *v* 3440-3350 cm^{-1} (NH-NH_2) groups and represented absorption bands at *v* 1735 and 1688 cm^{-1} for two carbonyl groups. Its ^{1}HNMR spectrum of **12a** denoted two singlet singles at δ 6.60 and 10.50 ppm showing the presence of one amino and one (NH) groups (with D_2O exchangeable). Furthermore, the compounds **12a-c** were condensed with dimethylformamide (DMF/ K_2CO_3) solution, [41, 49, 50] stirring and refluxing for a long time under thin layer chromatography (TLC) control afforded 3-substituted-5-methyl-2-((6-phenyl-4, 5-dihydropyridazin-3(2*H*)-ylidene) hydrazono) thiazolidin-4-one **13a-c** in good yield. The IR spectrum of **13a** demonstrated absorption bands around at *v* 3344 cm^{-1} for one (NH) and 1682 cm^{-1} for one carbonyl group. The ^{1}H-NMR spectrum of **13a** showing one singlet signals at δ 11.30 ppm for the one proton of one (NH) group (D_2O exchangeable) and The mass spectrum of **13a**, **13b** and **13c** indicated the molecular ion peak at *m/z* =377 (M^+, 90%), 391 (M^+, 86%), 329 (M^+, 94%), respectively. Additionally, the reaction mixture of (**9a-c**) and chloroacetyl-chloride [46] in ethanol with the existence of potassium hydroxide yielded the corresponding1-((3-substituted-5-methyl-4-oxothiazolidin-2-ylidene) amino)-6-chloro-5-phenyl-3, 4-dihydro-1*H*-azepine-2, 7-dione (**14a-c**). The IR spectra of (**14a**) revealed an absorption bands at *v* 1690, 1685 and 1680 cm^{-1} for three carbonyl groups, 1630 cm^{-1} for (C=N), 1585 cm^{-1} for (C=C) and 1185 cm^{-1} for (C-Cl). The ^{1}H-NMR spectrum of (**14a**) exposed one doublet signals appeared at δ 1.69 ppm for three protons of the methyl group and two triplets at δ 2.02 - 2.22 and 2.27 -2.35 ppm to four protons of ($2CH_2$) groups in the azepine ring and one quartet signals at δ 4.38 ppm for one proton of (CH) group in the thiazole ring. The NMR and MS spectra supported the suggested structures (cf. experimental and **Scheme 3**).



Scheme 3: Synthesis of thiopyran, thiazolidinone, hydrazon-hydrazide, pyridazine, azepine-2, 7-dione derivatives

3. BIOLOGICAL ACTIVITIES

3.1. Antimicrobial Activity

All compounds were tested *in vitro* to microbial activity (bacteria and fungi) and all the results were offered in Tables **1** and **2**. Numerous of the compounds were showing the best antimicrobial activity when compared with cefotaxime sodium (MIC = 1-4 μmol mL^{-1}) and nystatin (MIC 2-5 μmol mL^{-1}). The new compounds **13a-c**, **14a-c**, **12a-c** and **11a-c** proved the better effective as an antimicrobial activity to against Gram-positive bacteria; *Streptococcus pyogenes, Staphylococcus aureus,* and Gram-negative bacteria; *Klebsiella pneumoniae, Escherichia coli*. The MIC values in μmol mL^{-1} to the compounds were as the following: **13a-c** (1-5), **14 a-c** (1-6), **12a-c** (4-8) and **11a-c** (6-10). Also, some of the compounds as **10a-c**, **9a-c, 8a-c** and **5a-c** displayed moderate antimicrobial activities. Furthermore, the compounds **14a-c**, **13a-c**, **12a-c** and **11a-c** awarded a potent antifungal activity with MIC in μmol /cm^3 of **14a-c** (1-5), **13** (2-6), **12a-c** (4-8) and **11a-c** (6-10) when compared with the positive control, nystatin (MIC 2-5 μmol mL^{-1}). Some of the compounds showed moderate antifungal activity when compared with nystatin (MIC 2-5 μmol mL^{-1}): **10a-c** (8-12), **9a-c** (10-15), **8a-c** (13-17) and **5a-c** (15-19). The tested fungi were *Candida albicans, Curvularia lunata, Alternaria alternata,* and *Aspergillus niger.*

3.2. Structure-Activity Relationships (SAR's)

It is clear that the results as antimicrobial for the compounds synthesized in this manuscript show the following and can be discussed as follows according to previous studies and new scientific articles. [1-3, 10, 21, 31, 34, 41, 48]

1- The compounds of **1-4** give less activity as antimicrobial due to the absence of any heterocyclic ring such as 1, 2, 4-triazoles; 1, 3, 4-oxadiazoles; 1, 3, 4-thiadiazoles or thiazolidine ring.

2 - The compounds of **5-10** given medium activity as antimicrobial due to the presence of a single heterocyclic ring, such as 1, 2, 4-triazole; 1, 3, 4-oxadiazole; 1, 3, 4-thiadiazole or thiazolidine ring with a few heteroatoms of different elements, such as nitrogen, sulfur and oxygen atom.

3- The compounds of **11-14** give higher activity as antimicrobial due to the presence of more than one ring of the heterocyclic rings such as thiazolidine, thiopyran, pyridazine or azepine ring with many heteroatoms of different elements such as nitrogen, oxygen and sulfur.

Therefore, new heterocyclic compounds were prepared that contain many rings known for their biological activities as antimicrobial in order to increase the activities of these compounds. Moreover, the chemical structures of these compounds and its relationship to increasing biological activity (SAR's) as antimicrobial can be discussed as follows; the excellent antimicrobial activities were found to compounds; pyridazin-hydrazono-thiazolidinone (**13a-c**), oxothiazolidin-azepine-2,7-dione (**14a-c**), *N*-oxothiazolidin-hydrazon-hydrazide (**12a-c**), thiopyran-hydrazono-thiazolidin-4-one (**11a-c**) derivatives against the test microorganisms, because they contain; pyridazine, thiazolidinone, azepine and thiopyran rings as an essential nucleus with an increasing number of nitrogen, sulphur and oxygen atoms according to past and new scientific articles. [3, 31, 34, 41, 48] Also, the same compounds **13a-c**, **14a-c**, **12a-c** and **11a-c** possess highest antimicrobial activities because of the transformation of the thiosemicarbazide, butane-hydrazide or phenyl-butane-hydrazone-hydrazide groups into pyridazine, thiazolidine, azepine or thiopyran ring that are linked by the functional groups such as phenyl, benzoyl, ethyl, methyl, chloro, thioxo, carbonyl and amino group, thus these rings and functional groups are containing electrons donating that affect the eradication of many types of bacteria and fungi according to previous studies. [1-3, 10, 21, 31, 34, 41, 48] Also, some of the compounds **10a-c**, **9a-c**, **8a-c,** **5a-c** and **6a-c** exhibited moderate antimicrobial activity and the rest of the compounds showed a weak antimicrobial activity compared to the standard drugs (cefotaxime sodium and nystatin). Moreover, the pyridazine, thiazolidinone, azepine**,** thiopyran, 1, 2, 4-triazoles, 1, 3, 4-oxadiazoles and 1, 3, 4-thiadiazoles derivatives have effective as antimicrobial agents in previous articles. [1-3, 10, 21, 31, 34, 41, 48] In this article and previous articles generally, the bacteria and fungi types are influenced *via* this category of heterocyclic compounds. [1-3, 21, 49] Likewise, past results and our findings in this article corroborate the promising antimicrobial activity of pyridazin-hydrazono-thiazolidinone, oxothiazolidin-azepine-dione, *N*-oxothiazolidin-hydrazon-hydrazide, thiopyran-hydrazono-thiazolidinone derivatives which can be developed to the highest antimicrobial activities.

Table 1: Minimum inhibitory concentrations against bacteria of the new compounds

MIC (µmol mL-1)				
Compounds	**Microorganisms**			
	Gram-positive bacteria		**Gram-negative bacteria**	
	Streptococcus pyogenes	***Staphylococcus aureus***	***Klebsiella pneumoniae***	***E. coli***
1	30± 0.009	31± 0.005	29± 0.008	30± 0.006
2	29± 0.004	30± 0.006	28± 0.003	29± 0.007
3	28± 0.002	29± 0.001	27± 0.005	28± 0.004
4a	26± 0.006	27± 0.008	25± 0.009	26± 0.002
4b	25± 0.012	26± 0.014	24± 0.013	25± 0.018
4c	27± 0.009	28± 0.015	26± 0.012	27± 0.016
5a	18± 0.015	18± 0.007	16± 0.005	17± 0.013
5b	17± 0.002	18± 0.017	15± 0.014	16± 0.011
5c	18± 0.007	19± 0.005	17± 0.008	18± 0.009
6a	23± 0.012	24± 0.014	22± 0.016	23± 0.015
6b	22± 0.018	23± 0.013	21± 0.012	22± 0.014
6c	24± 0.019	25± 0.011	23± 0.017	24± 0.018
7a	20± 0.009	21± 0.018	19± 0.011	20± 0.012
7b	19± 0.013	20± 0.015	18± 0.013	19± 0.016
7c	21± 0.021	22± 0.023	20± 0.025	21± 0.022
8a	16± 0.027	17± 0.026	14± 0.024	15± 0.025
8b	15± 0.015	16± 0.018	13± 0.021	14± 0.028
8c	17± 0.023	18± 0.026	15± 0.025	15± 0.021
9a	13± 0.013	14± 0.014	11± 0.005	12± 0.008
9b	12± 0.027	13± 0.022	10± 0.029	11± 0.027
9c	14± 0.021	15± 0.025	12± 0.003	13± 0.004
10a	11± 0.031	12± 0.033	9± 0.032	10± 0.034
10b	10± 0.035	11± 0.037	8± 0.036	9± 0.038
10c	12± 0.011	12± 0.034	10± 0.032	11± 0.036
11a	9± 0.025	9± 0.029	7± 0.028	7± 0.026
11b	8± 0.041	9± 0.043	6± 0.042	7± 0.044
11c	9± 0.045	10± 0.047	7± 0.046	8± 0.043
12a	7± 0.047	7± 0.048	5± 0.035	5± 0.029
12b	6± 0.049	7± 0.045	4± 0.043	5± 0.046
12c	7± 0.051	8± 0.054	5± 0.053	6± 0.052
13a	3± 0.055	4± 0.058	1± 0.057	2± 0.056
13b	2± 0.054	3± 0.053	1± 0.055	2± 0.054
13c	4± 0.009	5± 0.011	2± 0.028	3± 0.037
14a	4± 0.052	5± 0.055	2± 0.059	3± 0.024
14b	3± 0.019	4± 0.021	1± 0.028	2± 0.031
14c	5± 0.022	6± 0.034	3± 0.041	4± 0.057
Cefotaxime sodium	**3**± 0.005	**4**± 0.004	**1**± 0.006	**2**± 0.009
Negative control	NI	NI	NI	NI

DMSO was used as the negative control and as the solvent for test compounds and the reference drug. NI – No inhibition

Table 2: Minimum inhibitory concentrations against fungi of the new compounds

MIC (µmol mL^{-1})				
Compounds	**Microorganisms**			
	Candida albicans	***Curvularia lunata***	***Alternaria alternata***	***Aspergillus niger***
1	26± 0.005	27± 0.002	28± 0.004	29± 0.006
2	25± 0.003	26± 0.008	27± 0.009	28± 0.007
3	24± 0.006	25± 0.003	26± 0.011	27± 0.013
4a	22± 0.012	23± 0.015	24± 0.013	25± 0.018
4b	21± 0.016	22± 0.018	23± 0.014	24± 0.011
4c	23± 0.005	24± 0.019	25± 0.013	26± 0.012
5a	15± 0.019	16± 0.017	17± 0.018	18± 0.015
5b	15± 0.006	16± 0.008	16± 0.012	17± 0.019
5c	16± 0.014	17± 0.012	18± 0.014	19± 0.017
6a	20± 0.021	21± 0.025	22± 0.022	23± 0.023
6b	19± 0.009	20± 0.015	21± 0.026	22± 0.028
6c	20± 0.027	21± 0.029	23± 0.008	24± 0.023
7a	18± 0.029	19± 0.024	20± 0.022	21± 0.025
7b	17± 0.017	18± 0.019	19± 0.021	20± 0.024
7c	18± 0.022	20± 0.026	20± 0.029	21± 0.018
8a	13± 0.031	14± 0.033	16± 0.032	17± 0.021
8b	13± 0.034	14± 0.037	15± 0.035	16± 0.038
8c	14± 0.028	15± 0.019	16± 0.025	17± 0.039
9a	11± 0.035	12± 0.038	13± 0.036	14± 0.034
9b	10± 0.033	11± 0.027	12± 0.015	13± 0.013
9c	12± 0.032	13± 0.035	14± 0.029	15± 0.028
10a	9± 0.042	9± 0.045	10± 0.038	11± 0.041
10b	8± 0.041	9± 0.022	10± 0.043	11± 0.032
10c	9± 0.036	10± 0.046	11± 0.048	12± 0.049
11a	6± 0.028	7± 0.031	9± 0.047	9± 0.042
11b	6± 0.051	7± 0.043	8± 0.052	9± 0.055
11c	7± 0.057	8± 0.059	9± 0.045	10± 0.016
12a	5± 0.058	5± 0.056	7± 0.029	7± 0.057
12b	4± 0.054	5± 0.052	6± 0.058	7± 0.044
12c	5± 0.062	6± 0.055	7± 0.064	8± 0.061
13a	3± 0.065	4± 0.068	5± 0.059	6± 0.042
13b	2± 0.059	3± 0.063	5± 0.052	5± 0.071
13c	4± 0.075	4± 0.061	5± 0.072	6± 0.073
14a	2± 0.055	3± 0.077	3± 0.074	4± 0.066
14b	1± 0.068	2± 0.076	3± 0.059	4± 0.078
14c	2± 0.049	3± 0.057	4± 0.079	5± 0.037
Nystatin	**2**± 0.008	**3**± 0.014	**4**± 0.012	**5**± 0.007
Negative control	NI	NI	NI	NI

DMSO was used as the negative control and as the solvent for test compounds and the reference drug. NI- No inhibition

4.1. EXPERIMENTAL SECTION

*4.2. **Materials***

All materials used were obtained from Sigma Aldrich (Saint Lewis, USA).

*4.3. **Equipment's***

All melting points are in degree centigrade (uncorrected) and were determined on Gallenkamp electric melting point apparatus. TLC analysis was carried out on silica gel 60 F_{254} precoated aluminum sheets. The IR spectra were recorded (KBr) on a Perkin–Elmer 1430 spectrometer (λ, cm^{-1}) in National Research Centre, Egypt. ^{1}H and ^{13}C-NMR Spectra were measured on JEOL-ECA 500 and JEOL JNM-LA-400 FT NMR Spectrometers at 500, 125 MHz, respectively, using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 as the solvent at the Microanalytical Center in National Research Centre, Egypt. The mass spectra (EI) were recorded on GCMS-QP 1000 EX (Shimadzu) at National Research Centre, Egypt. Elemental analyses (C, H and N) were carried out at the Microanalytical Center in National Research Centre, Egypt. The elemental analyses were found to agree favorably with the calculated values. Biological evaluations were done by the antimicrobial unit, Department of Chemistry of Natural and Microbial Products, National Research Centre, Egypt.

*4.4. Synthesis of **Ethyl 4-oxo-4-phenylbutanoate*** **(2)**, [41]

A mixture of 3-benzoylpropionic acid **1** (1.78g, 0.01 mol) in absolute ethanol (40 ml) containing a few drops of concentrated sulphuric acid was refluxed for 3-5h under control (TLC). The oil formed was separated by using a rotary system and the purification by sodium sulphate and chloroform to give compound **2** as a liquid oil in 75% yield, IR (ν, cm^{-1}): 3055 (CH aryl), 2960 (CH alkyl), 1790 (C=O), 1750 (C=O), 1570 (C=C). ^{1}H NMR (DMSO-d_6, ppm) δ 1.30 (t, 3 H, J = 4.20 Hz, CH_3), 2.15 (t, 2 H, J = 4.25 Hz, CH_2), 3.70 (t, 2 H, J = 4.27 Hz, CH_2), 4.12 (q, 2 H, J = 4.29 Hz, CH_2), 7.55-7.92 (m, 5H, phenyl); ^{13}C NMR (DMSO-d_6) δ 20.1 (1C, CH_3), 30.5, 34.6, 63.4 (3C, $3CH_2$), 128.1, 128.5,130.9, 134.8 (6 C, Ar-C), 168.7, 183.5 (2C, 2C=O); MS (70 eV, %) *m/z* 206 (M^+, 100%); Anal. Calc. (Found) for $C_{12}H_{14}O_3$ (206.24): C, 69.89 (69.80); H, 6.84 (6.78).

*4.5. Synthesis of **4-oxo-4-phenylbutanehydrazide*** **(3)**

A mixture of **2** (2.10 mL, 0.01 mol) and hydrazine monohydrate (0.01 mol) (80-90%) in absolute ethanol (30 mL) was stirred under refluxed for 2-4h. The reaction mixture was then allowed to

cool to room temperature. The solid was filtered, washed with methanol, dried, and crystallized from dioxane as yellow crystals, in 90% yield, m. p. 170-172 °C. IR (KBr): ν_{max} = 3405-3325 (brs, NH, NH_2), 3045 (CH, aryl), 2952 (CH, alkyl), 1722, 1675 (2C=O), 1578 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.22-2.27 (t, 2 H, J = 5.48 Hz, CH_2), 3.20-3.25 (t, 2 H, J = 5.49 Hz, CH_2), 6.10 (br, 2H, NH_2, D_2O exchangeable), 7.55-7.92 (m, 5H, Ar-H), 9.08 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 30.1, 33.8 (2C, $2CH_2$), 128.4, 128.9, 131.5, 134.8 (6C, Ar-C), 174.7, 182.2 (2C, 2C=O); MS (70 eV): m/z = 192 (M^+, 100%); Anal. Calc. (Found) for $C_{10}H_{12}N_2O_2$ (192.22): C, 62.49 (62.40); H, 6.29 (6.21); N, 14.57 (14.68).

4.6. Synthesis of ***N-substituted-2-(4-oxo-4-phenylbutanoyl) hydrazine-1-carbothioamide*** **(4a-c)**

General Procedure: A mixture of **3** (1.92g, 0.01 mol) and the appropriate isothiocyanate (0.01 mol), namely phenyl-, benzyl-, and ethylisothiocyanate, in absolute ethanol (30 mL) was refluxed for 4-7h and then left to cool. The precipitate formed was filtered off, dried, and crystallized from the appropriate solvent to give **4a-c**.

4.7. Synthesis of ***2-(4-oxo-4-phenylbutanoyl)-N-phenylhydrazine-1-carbothioamide*** **(4a)**

The compound was obtained from the reaction of **3** with phenylisothiocyanate (1.20 mL, 0.01 mol), as white crystals, crystallized from methanol in 88% yield, m. p. 215-217 °C. IR (KBr): ν_{max} = 3330, 3240, 3155 (br, 3NH), 3050 (CH aryl), 2960 (CH alkyl), 1725, 1680 (2C=O), 1585 (C=C), 1355 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.25-2.30 (t, 2 H, J = 5.50 Hz, CH_2), 3.05-3.10 (t, 2H, J = 5.56 Hz, CH_2), 7.05-7.90 (m, 10 H, Ar-H), 9.90, 10.70, 11.60 (br, 3H, 3NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ =31.5, 34.6 (2C, $2CH_2$), 125.4, 127.2, 128.3, 128.7, 129.1, 132.6, 135.2, 137.8 (12C, Ar-C), 172.3, 178.5 (2C, 2C=O), 182.8 (1C, C=S); MS (70 eV): m/z = 327 (M^+, 100 %); Anal. Calc. (Found) for $C_{17}H_{17}N_3O_2S$ (327.40): C, 62.37 (62.30); H, 5.23 (5.18); N, 12.83 (12.90).

4.8. Synthesis of ***N-benzyl-2-(4-oxo-4-phenylbutanoyl) hydrazine-1-carbothioamide*** **(4b)**

The compound was obtained from the reaction of **3** with benzylisothiocyanate (1.32 mL, 0.01 mol), as yellow crystals, crystallized from dioxane in 75% yield, m. p. 198-200 °C. IR (KBr): ν_{max} = 3333, 3242, 3157 (br, 3NH), 3054 (CH aryl), 2963 (CH alkyl), 1720, 1684 (2C=O), 1588 (C=C), 1357 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.29-2.34 (t, 2H, J = 5.55 Hz, CH_2), 3.10-

3.15 (t, 2H, J = 5.58 Hz, CH_2), 4.55 (s, 2H, CH_2), 7.20-7.95 (m, 10H, Ar-H), 9.82, 10.62, 11.55 (br, 3H, 3NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 31.3, 34.5, 55.1 (3C, 3CH_2), 125.8, 126.2, 127.6, 128.9, 129.1, 132.9, 135.5, 138.2 (12C, Ar-C), 172.8, 178.9 (2C, 2C=O), 183.2 (1C, C=S); MS (70 eV): m/z = 341 (M^+, 90%); Anal. Calc. (Found) for $C_{18}H_{19}N_3O_2S$ (341.43): C, 63.32 (63.25); H, 5.61 (5.68); N, 12.31 (12.24).

4.9. Synthesis of ***N-ethyl-2-(4-oxo-4-phenylbutanoyl) hydrazine-1-carbothioamide*** **(4c)**

The compound was obtained from the reaction of **3** with ethylisothiocyanate (0.87 mL, 0.01 mol), as yellowish crystals, crystallized from chloroform in 78% yield, m. p. 185-187 °C. IR (KBr): ν_{max} = 3329, 3239, 3148 (br, 3NH), 3048 (CH aryl), 2958 (CH alkyl), 1718, 1679 (2C=O), 1582 (C=C), 1350 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.35-1.41 (t, 3H, J = 5.62 Hz, CH_3), 2.20-2.26 (t, 2H, J = 5.52 Hz, CH_2), 3.01-3.06 (t, 2 H, J = 5.54 Hz, CH_2), 4.70 - 4.77 (q, 2H, J = 5.60 Hz, CH_2), 7.46 -7.95 (m, 5H, Ar-H), 9.75, 10.58, 11.50 (br, 3H, 3NH, D_2O exchangeable).^{13}C NMR (DMSO-d_6) δ = 20.1 (1C, CH_3), 31.1, 34.2, 50.4 (3C, 3CH_2), 128.3, 128.7, 133.5, 136.2 (6C, Ar-C), 170.5, 176.4 (2C, 2C=O), 180.6 (1C, C=S); MS (70 eV): m/z = 279 (M^+, 95%); Anal. Calc. (Found) for $C_{13}H_{17}N_3O_2S$ (279.36): C, 55.89 (55.80); H, 6.13 (6.19); N, 15.04 (15.12).

4.10. Synthesis of ***3-(4-substituted-5-thioxo-4, 5-dihydro-1H-1, 2, 4-triazol-3-yl)-1-phenyl propan-1-one*** **(5a-c)**

General Procedure: A mixture of suitable thiosemicarbazides **4a-c** (0.01 mol) in aqueous sodium hydroxide (45 mL, 2*N*) was heated and refluxed under stirring for 4 -7h. The reaction mixture was then cooled and neutralized with dilute hydrochloric acid. The solid precipitate obtained was filtered off, washed with water several times, dried, and crystallized from the appropriate solvent to give **5a-c**.

4.11. Synthesis of ***1-phenyl-3-(4-phenyl-5-thioxo-4, 5-dihydro-1H-1, 2, 4-triazol-3-yl) propan-1-one*** **(5a)**

The compound was obtained from the reaction of thiosemicarbazides **4a** (3.27g, 0.01 mol) with aqueous sodium hydroxide (*2N*), as yellowish crystals, crystallized from benzene in 85% yield, m. p. 237-239 °C. IR (KBr): ν_{max} = 3305 (br, NH), 3054 (CH aryl), 2947 (CH alkyl), 1715 (C=O), 1617 (C=N), 1590 (C=C), 1345 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 3.03-3.10 (t, 2H, J = 5.60 Hz, CH_2), 3.24 -3.31 (t, 2H, J = 5.63 Hz, CH_2), 7.28-7.95 (m, 10H, Ar-H), 12.10 (br, 1H, NH,

D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 30.1, 33.4 (2C, $2CH_2$), 128.1, 128.4, 128.6, 129.5, 129.9, 131.3, 132.8, 135.6, 150.5 (13C, Ar-C), 168.7 (1C, C=S), 180.8 (1C, C=O); MS (70 eV): *m/z* = 309 (M^+, 100%); Anal. Calc. (Found) for $C_{17}H_{15}N_3OS$ (309.39): C, 66.00 (66.10); H, 4.89 (4.80); N, 13.58 (13.52).

4.12. Synthesis of ***3-(4-benzyl-5-thioxo-4, 5-dihydro-1H-1, 2, 4-triazol-3-yl)-1-phenylpropan-1-one*** **(5b)**

The compound was obtained from the reaction of thiosemicarbazides **4b** (3.41g, 0.01 mol) with aqueous sodium hydroxide (2*N*), as brownish crystals, crystallized from toluene in 80% yield, m. p. 225-227 °C. IR (KBr): ν_{max} = 3310 (br, NH), 3052 (CH aryl), 2944 (CH alkyl), 1719 (C=O), 1619 (C=N), 1588 (C=C), 1348 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.08-3.15 (t, 2H, *J* = 5.65 Hz, CH_2), 3.28 -3.35 (t, 2H, *J* = 5.64 Hz, CH_2), 4.82 (s, 2H, CH_2), 7.30 -7.97 (m, 10H, Ar-H), 12.20 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 30.5, 32.1, 51.7 (3C, $3CH_2$), 126.2, 127.1, 128.3, 128.9, 129.3, 131.7, 133.5, 134.2, 155.3 (13C, Ar-C), 170.2 (1C, C=S), 181.5 (1C, C=O); MS (70 eV): *m/z* = 323 (M^+, 92%); Anal. Calc. (Found) for $C_{18}H_{17}N_3OS$ (323.41): C, 66.85 (66.78); H, 5.30 (5.37); N, 12.99 (12.91).

4.13. Synthesis of ***3-(4-ethyl-5-thioxo-4, 5-dihydro-1H-1, 2, 4-triazol-3-yl)-1-phenylpropan-1-one*** **(5c)**

The compound was obtained from the reaction of thiosemicarbazides **4c** (2.79g, 0.01 mol) with aqueous sodium hydroxide (2*N*), as yellowish crystals, crystallized from xylene in 86% yield, m. p. 207-209 °C. IR (KBr): ν_{max} = 3315 (br, NH), 3057 (CH aryl), 2946 (CH alkyl), 1722 (C=O), 1621 (C=N), 1592 (C=C), 1351 (C=S) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.30-1.36 (t, 3H, *J* = 5.66 Hz, CH_3), 3.12-3.20 (t, 2H, *J* = 5.64 Hz, CH_2), 3.31 -3.38 (t, 2H, *J* = 5.67 Hz, CH_2), 4.66 - 4.72 (q, 2H, *J* = 5.69 Hz, CH_2), 7.41-7.90 (m, 5H, Ar-H), 12.30 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 21.2 (1C, CH_3), 30.8, 32.4, 52.3 (3C, $3CH_2$), 128.4, 128.7, 132.5, 135.2, 154.4 (7C, Ar-C), 173.5 (1C, C=S), 184.2 (1C, C=O); MS (70 eV): *m/z* = 261 (M^+, 96%); Anal. Calc. (Found) for $C_{13}H_{15}N_3OS$ (261.34): C, 59.75 (59.82); H, 5.79 (5.70); N, 16.08 (16.01).

4.14. Synthesis of ***3-(5-(substituted-amino)-1, 3, 4-oxadiazol-2-yl)-1-phenylpropan-1-one*** **(6a-c)**

General Procedure: A mixture of the appropriate thiosemicarbazides **4a-c** (0.01mol) and excess yellow mercuric oxide (3.25g, 0.015mol), in ethanol (40 mL) was refluxed for 6-10h. The reaction mixture was allowed to cool to room temperature (to allow the sedimentation of the black mercuric sulphide), was filtered, and the mercuric sulphide was washed with ethanol. The filtrate and alcoholic washing were combined, treated with water until permenant turbidity existed, and allowed to stand overnight. The product was separated and crystallized from the proper solvent to give **6a-c**.

4.15. Synthesis of ***1-phenyl-3-(5-(phenylamino)-1, 3, 4-oxadiazol-2-yl) propan-1-one*** **(6a)**

The compound was obtained from the reaction of thiosemicarbazides **4a** (3.27g, 0.01 mol) with mercuric oxide (3.25g, 0.015mol), as brownish crystals, crystallized from dioxane in 79% yield, m. p. 256-258 °C. IR (KBr): ν_{max} = 3260 (br, NH), 3058 (CH aryl), 2935 (CH alkyl), 1725 (C=O), 1622 (C=N), 1587 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.84-2.90 (t, 2H, J = 5.58 Hz, CH_2), 2.95 -3.02 (t, 2H, J = 5.57 Hz, CH_2), 7.15-7.92 (m, 10H, Ar-H), 11.20 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 28.5, 37.2 (2C, $2CH_2$), 122.7, 123.5, 128.4, 128.8, 129.7, 132.1, 135.6, 137.8, 151.4, 158.5 (14C, Ar-C), 186.1 (1C, C=O); MS (70 eV): *m/z* = 293 (M^+, 98%); Anal. Calc. (Found) for $C_{17}H_{15}N_3O_2$ (293.33): C, 69.61 (69.69); H, 5.15 (5.10); N, 14.33 (14.26).

4.16. Synthesis of ***3-(5-(benzylamino)-1, 3, 4-oxadiazol-2-yl)-1-phenylpropan-1-one*** **(6b)**

The compound was obtained from the reaction of thiosemicarbazides **4b** (3.41g, 0.01 mol) with mercuric oxide (3.25g, 0.015mol), as yellowish crystals, crystallized from acetone in 72% yield, m. p. 246-248 °C. IR (KBr): ν_{max} = 3265 (br, NH), 3055 (CH aryl), 2940 (CH alkyl), 1723 (C=O), 1623 (C=N), 1588 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.80-2.86 (t, 2H, J = 5.56 Hz, CH_2), 2.90- 2.97 (t, 2H, J = 5.55 Hz, CH_2), 4.74 (s, 2H, CH_2), 7.35-7.96 (m, 10H, Ar-H), 10.80 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 27.8, 36.5, 51.5 (3C, $3CH_2$), 126.4, 127.2, 128.3, 128.7, 129.1, 132.5, 136.2, 138.5, 152.1, 158.8 (14C, Ar-C), 187.3 (1C, C=O); MS (70 eV): *m/z* = 307 (M^+, 90%); Anal. Calc. (Found) for $C_{18}H_{17}N_3O_2$ (307.35): C, 70.34 (70. 25); H, 5.58 (5.50); N, 13.67 (13.75).

4.17. Synthesis of ***3-(5-(ethylamino)-1, 3, 4-oxadiazol-2-yl)-1-phenylpropan-1-one*** **(6c)**

The compound was obtained from the reaction of thiosemicarbazides **4c** (2.79g, 0.01 mol) with mercuric oxide (3.25g, 0.015mol), as yellow crystals, crystallized from methanol in75% yield, m. p. 230-232 °C. IR (KBr): ν_{max} = 3255 (br, NH), 3051 (CH aryl), 2942 (CH alkyl), 1726 (C=O), 1619 (C=N), 1586 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.25-1.31 (t, 3H, J = 5.62 Hz, CH_3), 2.80-2.87 (t, 2H, J = 5.61 Hz, CH_2), 2.93 -3.01 (t, 2 H, J = 5.63 Hz, CH_2), 4.24 - 4.30 (q, 2H, J = 5.64 Hz, CH_2), 7.50 -7.96 (m, 5H, Ar-H), 10.40 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 22.4 (1C, CH_3), 27.9, 34.8, 50.2 (3C, $3CH_2$), 128.1, 128.6, 131.9, 137.4, 155.2, 158.3 (8C, Ar-C), 185.6 (1C, C=O); MS (70 eV): *m/z* = 245 (M^+, 95%); Anal. Calc. (Found) for $C_{13}H_{15}N_3O_2$ (245.28): C, 63.66 (63.57); H, 6.16 (6.10); N, 17.13 (17.20).

4.18. Synthesis of ***3-(5-(substituted-amino)-1, 3, 4-thiadiazol-2-yl)-1-phenylpropan-1-one*** **(7a-c)**

General Procedure: Phosphorus-oxychloride (35 mL) was added to the appropriate thiosemi-carbazides **4a-c** (0.01 mol), and the mixture was refluxed for 4-6h. The mixture was then evaporated in vacuo, and the residue was washed with dilute ammonium hydroxide solution and water. The solid obtained was filtered off, dried, and crystallized from the suitable solvent to give **7a-c**.

4.19. Synthesis of ***1-phenyl-3-(5-(phenylamino)-1, 3, 4-thiadiazol-2-yl) propan-1-one*** **(7a)**

The compound was obtained from the reaction of thiosemicarbazides **4a** (3.27g, 0.01 mol) with phosphorus oxychloride, as yellowish crystals, crystallized from chloroform in 87% yield, m. p. 283-285 °C. IR (KBr): ν_{max} = 3245 (br, NH), 3052 (CH aryl), 2944 (CH alkyl), 1727 (C=O), 1620 (C=N), 1580 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.80-2.86 (t, 2H, J = 5.55 Hz, CH_2), 2.91-2.95 (t, 2H, J = 5.54 Hz, CH_2), 7.20 -7.97 (m, 10H, Ar-H), 10.70 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 27.6, 37.8 (2C, $2CH_2$), 121.9, 124.3, 127.9, 128.5, 129.8, 132.5, 136.4, 138.2, 155.1, 161.4 (14C, Ar-C), 183.8 (1C, C=O); MS (70 eV): *m/z* = 309 (M^+, 100%); Anal. Calc. (Found) for $C_{17}H_{15}N_3OS$ (309.39): C, 66.00 (66.12); H, 4.89 (4.80); N, 13.58 (13.49).

4.20. Synthesis of ***3-(5-(benzylamino)-1, 3, 4-thiadiazol-2-yl)-1-phenylpropan-1-one*** **(7b)**

The compound was obtained from the reaction of thiosemicarbazides **4b** (3.41g, 0.01 mol) with phosphorus oxychloride, as brownish crystals, crystallized from dimethyl-formamide in 80% yield, m. p. 274-276 °C. IR (KBr): ν_{max} = 3268 (br, NH), 3053 (CH aryl), 2942 (CH alkyl), 1728 (C=O), 1625 (C=N), 1591 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.76-2.80 (t, 2H, J = 5.66 Hz, CH_2), 2.87 - 2.91 (t, 2H, J = 5.68 Hz, CH_2), 4.80 (s, 2H, CH_2), 7.30 -7.92 (m, 10H, Ar-H), 10.65 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 26.9, 37.1, 53.4 (3C, $3CH_2$), 125.8, 127.5, 128.1, 128.6, 129.3, 133.4, 137.5, 139.2, 157.2, 162.1 (14C, Ar-C), 184.2 (1C, C=O); MS (70 eV): *m/z* = 323 (M^+, 84%); Anal. Calc. (Found) for $C_{18}H_{17}N_3OS$ (323.41): C, 66.85 (66.75); H, 5.30 (5.38); N, 12.99 (12.90).

4.21. Synthesis of ***3-(5-(ethylamino)-1, 3, 4-thiadiazol-2-yl)-1-phenylpropan-1-one*** **(7c)**

The compound was obtained from the reaction of thiosemicarbazides **4c** (2.79g, 0.01 mol) with phosphorus oxychloride, as yellowish crystals, crystallized from ethanol in 84% yield, m. p. 265-267 °C. IR (KBr): ν_{max} = 3275 (br, NH), 3057 (CH aryl), 2944 (CH alkyl), 1723 (C=O), 1615 (C=N), 1582 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.20-1.27 (t, 3H, J = 5.68 Hz, CH_3), 2.77-2.85 (t, 2H, J = 5.69 Hz, CH_2), 2.89 -2.95 (t, 2H, J = 5.67Hz, CH_2), 4.31 - 4.37 (q, 2H, J = 5.63 Hz, CH_2), 7.55 -7.98 (m, 5H, Ar-H), 10.52 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 22.8 (1C, CH_3), 28.3, 35.9, 50.4 (3C, $3CH_2$), 128.3, 128.8, 132.2, 136.5, 157.5, 162.7 (8C, Ar-C), 185.9 (1C, C=O); MS (70 eV): *m/z* = 261 (M^+, 97%); Anal. Calc. (Found) for $C_{13}H_{15}N_3OS$ (261.34): C, 59.75 (59.66); H, 5.79 (5.70); N, 16.08 (16.16).

4.22. Synthesis of ***N'-(3-substituted-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutanehydrazide*** **(8a-c)**

General Procedure: A mix of the appropriate thiosemicarbazides **4a-c** (0.01 mol), ethylbromo-acetate (1.67mL, 0.01 mol), and anhydrous sodium acetate (1.23g, 0.015 mol) in absolute ethanol (35 mL) was refluxed for 5-8h under control (TLC). The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The solid obtained was filtered off, dried, and crystallized from the proper solvent to give **8a-c**.

4.23. Synthesis of ***4-oxo-N'-(4-oxo-3-phenylthiazolidin-2-ylidene)-4-phenylbutanehydrazide*** **(8a)**

The compound was obtained from the reaction of thiosemicarbazides **4a** (3.27g, 0.01 mol) with ethyl-bromoacetate, as white crystals, crystallized from n-hexane in 76% yield, m. p. 313-315 °C. IR (KBr): ν_{max} = 3315 (br, NH), 3070 (CH aryl), 2958 (CH alkyl), 1730, 1690, 1683 (3C=O), 1617 (C=N), 1592 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.70 - 2.77 (t, 2H, J = 5.70 Hz, CH_2), 3.25 -3.31 (t, 2H, J = 5.71 Hz, CH_2), 4.25 (s, 2H, CH_2, thiazole), 7.40 -7.98 (m, 10H, Ar-H), 10.90 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 30.1, 31.7, 34.5 (3C, $3CH_2$), 127.5, 127.8, 128.4, 128.8, 129.2, 132.7, 135.4, 137.1, 146.5 (13C, Ar-C), 165.5, 170.8, 185.4 (3C, 3C=O); MS (70 eV): *m/z* = 367 (M^+, 100%); Anal. Calc. (Found) for $C_{19}H_{17}N_3O_3S$ (367.42): C, 62.11 (62.20); H, 4.66 (4.60); N, 11.44 (11.35).

4.24. Synthesis of ***N'-(3-benzyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutanehydrazide*** **(8b)**

The compound was obtained from the reaction of thiosemicarbazides **4b** (3.41g, 0.01 mol) with ethyl-bromoacetate, as brownish crystals, crystallized from benzene in 73% yield, m. p. 302-305 °C. IR (KBr): ν_{max} = 3320 (br, NH), 3072 (CH aryl), 2960 (CH alkyl),1733, 1692, 1685 (3C=O), 1615 (C=N), 1595 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.66 - 2.73 (t, 2H, J = 5.72 Hz, CH_2), 3.28 -3.35 (t, 2H, J = 5.73 Hz, CH_2), 4.31 (s, 2H, CH_2, thiazole), 5.75 (s, 2H, CH_2), 7.32 -7.92 (m, 10H, Ar-H), 10.85 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 30.7, 32.2, 35.4, 51.6 (4C, $4CH_2$), 126.6, 127.3, 128.1, 128.5, 128.9, 132.4, 135.8, 137.5, 152.7 (13C, Ar-C), 166.1, 171.3, 185.8 (3C, 3C=O); MS (70 eV): *m/z* = 381(M^+, 92%); Anal. Calc. (Found) for $C_{20}H_{19}N_3O_3S$ (381.45): C, 62.98 (62.90); H, 5.02 (5.08); N, 11.02 (11.10).

4.25. Synthesis of ***N'-(3-ethyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutanehydrazide*** **(8c)**

The compound was obtained from the reaction of thiosemicarbazides **4c** (2.79g, 0.01 mol) with ethyl-bromoacetate, as yellowish crystals, crystallized from methanol in 74% yield, m. p. 293-295 °C. IR (KBr): ν_{max} = 3325 (br, NH), 3075 (CH aryl), 2965 (CH alkyl),1735, 1695, 1688 (3C=O), 1618 (C=N), 1593 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ =1.24-1.32 (t, 3H, J = 5.74 Hz, CH_3), 2.63- 2.70 (t, 2H, J = 5.75 Hz, CH_2), 3.31 -3.38 (t, 2H, J = 5.77 Hz, CH_2), 4.35 (s, 2H, CH_2, thiazole), 4.91- 4.97 (q, 2H, J = 5.73 Hz, CH_2), 7.52 -7.95 (m, 5H, Ar-H), 10.75 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 23.4 (1C, CH_3), 30.9, 32.6, 36.1, 37.4 (4C, $4CH_2$), 128.4, 128.9, 131.7, 134.5, 153.2 (7C, Ar-C), 168.1, 172.5, 186.2 (3C, 3C=O); MS (70 eV): *m/z* =

319 (M^+, 96%); Anal. Calc. (Found) for $C_{15}H_{17}N_3O_3S$ (319.38): C, 56.41 (56.52); H, 5.37 (5.44); N, 13.16 (13.07).

*4.26. Synthesis of (**N'-(3-substituted-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenyl butane hydrazide*** **(9a-c)**

General Procedure: A mix of the suitable thiosemicarbazides **4a-c** (0.01 mol), *α*-bromopropionic acid (0.9 mL, 0.01 mol), and anhydrous sodium acetate (1.23g, 0.015 mol) in absolute ethanol (35 mL) was heated and refluxed for 6-9h. The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The solid obtained was filtered off, dried, and crystallized from the appropriate solvent to give **9a-c**.

*4.27. Synthesis of **N'-(5-methyl-4-oxo-3-phenylthiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazide*** **(9a)**

The compound was obtained from the reaction of thiosemicarbazides **4a** (3.27g, 0.01 mol) with *α*-bromopropionic acid, as yellow crystals, crystallized from methanol in 75% yield, m. p. 322-324 °C. IR (KBr): ν_{max} = 3325 (br, NH), 3075 (CH aryl), 2965 (CH alkyl), 1735, 1693, 1685 (3C=O), 1624 (C=N), 1590 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.75-1.78 (d, 3H, J = 5.80 Hz, CH_3), 2.68-2.74 (t, 2H, J = 5.78 Hz, CH_2), 3.28 -3.35 (t, 2H, J = 5.79 Hz, CH_2), 4.50 (q, 1H, CH, J = 5.77 Hz, thiazole), 7.39 -7.97 (m, 10H, Ar-H), 10.71 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 24.1 (1C, CH_3), 31.8, 34.2 (2C, $2CH_2$), 57.5 (1C, CH, thiazole), 127.7, 127.9, 128.3, 128.7, 129.1, 132.5, 135.8, 136.4, 150.1 (13C, Ar-C), 166.2, 171.1, 186.3(3C, 3C=O); MS (70 eV): m/z = 381 (M^+, 100%); Anal. Calc. (Found) for $C_{20}H_{19}N_3O_3S$ (381.45): C, 62.98 (62.90); H, 5.02 (5.10); N, 11.02 (11.11).

*4.28. Synthesis of (**N'-(3-benzyl-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazide*** **(9b)**

The compound was obtained from the reaction of thiosemicarbazides **4b** (3.41g, 0.01 mol) with *α*-bromopropionic acid, as yellowish crystals, crystallized from dioxane in 71% yield, m. p. 331-333 °C. IR (KBr): ν_{max} = 3320 (br, NH), 3070 (CH aryl), 2960 (CH alkyl), 1730, 1690, 1680 (3C=O), 1620 (C=N), 1585 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.80-1.83 (d, 3H, J = 5.85 Hz, CH_3),

2.60- 2.66 (t, 2H, J = 5.82 Hz, CH_2), 3.31 -3.38 (t, 2H, J = 5.84 Hz, CH_2), 4.55 (q, 1H, CH, J = 5.81 Hz, thiazole), 5.70 (s, 2H, CH_2), 7.22 -7.90 (m, 10H, Ar-H), 10.76 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 23.8 (1C, CH_3), 32.1, 34.8, 39.2 (3C, $3CH_2$), 56.2 (1C, CH, thiazole), 127.2, 127.8, 128.1, 128.5, 128.9, 132.8, 135.4, 136.1, 150.7 (13C, Ar-C), 168.1, 172.5, 187.4(3C, 3C=O); MS (70 eV): m/z = 395 (M^+, 88%); Anal. Calc. (Found) for $C_{21}H_{21}N_3O_3S$ (395.48): C, 63.78 (63.70); H, 5.35 (5.42); N, 10.63 (10.70).

4.29. Synthesis of ***N'-(3-ethyl-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazide*** **(9c)**

The compound was obtained from the reaction of thiosemicarbazides **4c** (2.79g, 0.01 mol) with α-bromopropionic acid, as white crystals, crystallized from tetrahydrofuran in 82% yield, m. p. 341-343 °C. IR (KBr): ν_{max} = 3318 (br, NH), 3066 (CH aryl), 2957 (CH alkyl), 1727, 1688, 1678 (3C=O), 1617 (C=N), 1579 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.27-1.35 (t, 3H, J = 5.82 Hz, CH_3), 1.86 - 1.90 (d, 3H, J = 5.83 Hz, CH_3), 2.65 - 2.71 (t, 2H, J = 5.87 Hz, CH_2), 3.28 -3.35 (t, 2H, J = 5.87 Hz, CH_2), 4.48 (q, 1H, CH, J = 5.86 Hz, thiazole), 4.85 - 4.91 (q, 2H, J = 5.80 Hz, CH_2), 7.55-7.98 (m, 5H, Ar-H), 10.80 (br, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6) δ = 18.7, 24.5 (2C, $2CH_3$), 31.9, 34.5, 35.7 (3C, $3CH_2$), 55.8 (1C, CH, thiazole), 128.3, 128.8, 132.7, 137.2, 153.4 (7C, Ar-C), 168.6, 172.8, 187.9 (3C, 3C=O); MS (70 eV): m/z = 333 (M^+, 94%); Anal. Calc. (Found) for $C_{16}H_{19}N_3O_3S$ (333.41): C, 57.64 (57.55); H, 5.74 (5.80); N, 12.60 (12.68).

4.30. Synthesis of ***N-(3-substituted-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazonoyl chloride*** **(10a-c)**

General Procedure: A mixture of **9a** (3.81g, 0.01 mol) or **9b** (3.95g, 0.01 mol) or **9c** (3.33g, 0.01 mol) in dry dioxane (35 mL) was treated with 25 mL of phosphorus oxy-chloride, and the mixture was stirred under reflux for 6-8h. The reaction mixture was allowed to cool to room temperature. Then, it was poured into cold water (100 mL), whereby a solid was separated, filtered off, and crystallized from a suitable solvent to give **10a-c**, respectively.

4.31. Synthesis of ***N-(5-methyl-4-oxo-3-phenylthiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazonoyl chloride*** **(10a)**

The compound was obtained from the reaction of **9a** with phosphorus oxy-chloride, as yellowish crystals, crystallized from DMF in 90% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3065 (CH aryl), 2960 (CH alkyl), 1732, 1690, (2C=O), 1628 (C=N), 1592 (C=C), 1174 (C-Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.79 - 1.82 (d, 3H, J = 5.88 Hz, CH_3), 2.71 - 2.77 (t, 2H, J = 5.83 Hz, CH_2), 3.32 -3.39 (t, 2H, J = 5.85 Hz, CH_2), 4.45 (q, 1H, CH, J = 5.82 Hz, thiazole), 7.36 -7.94 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 24.5 (1C, CH_3), 31.6, 33.9 (2C, $2CH_2$), 57.2 (1C, CH, thiazole), 127.5, 127.8, 128.5, 128.8, 129.2, 132.7, 135.9, 136.6, 152.3, 155.5 (14C, Ar-C), 172.3, 185.1 (2C, 2C=O); MS (70 eV): *m/z* = 399 (M^+, 100%); Anal. Calc. (Found) for $C_{20}H_{18}ClN_3O_2S$ (399.89): C, 60.07 (60.15); H, 4.54 (4.48); N, 10.51 (10.62).

4.32. Synthesis of ***N-(3-benzyl-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazonoyl chloride*** **(10b)**

The compound was obtained from the reaction of **9b** with phosphorus oxy-chloride, as brownish crystals, crystallized from dioxane in 83% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3062 (CH aryl), 2958 (CH alkyl), 1730, 1687, (2C=O), 1625 (C=N), 1588 (C=C), 1170 (C-Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.81- 1.85 (d, 3H, J = 5.87 Hz, CH_3), 2.75 - 2.82 (t, 2H, J = 5.86 Hz, CH_2), 3.35 -3.42 (t, 2H, J = 5.84 Hz, CH_2), 4.47 (q, 1H, CH, J = 5.85 Hz, thiazole), 5.50 (s, 2H, CH_2), 7.33-7.92 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 24.7 (1C, CH_3), 30.8, 32.5, 38.6 (3C, $3CH_2$), 56.7 (1C, CH, thiazole), 127.1, 127.5, 128.4, 128.7, 128.9, 132.4, 135.2, 136.4, 152.8, 156.1 (14C, Ar-C), 172.6, 185.5 (2C, 2C=O); MS (70 eV): *m/z* = 413 (M^+, 90%); Anal. Calc. (Found) for $C_{21}H_{20}ClN_3O_2S$ (413.92): C, 60.94 (60.85); H, 4.87 (4.80); N, 10.15 (10.24).

4.33. Synthesis of ***N-(3-ethyl-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazonoyl chloride*** **(10c)**

The compound was obtained from the reaction of **9c** with phosphorus oxy-chloride, as yellowish crystals, crystallized from acetone in 85% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3069 (CH aryl), 2962 (CH alkyl), 1733, 1684, (2C=O), 1627 (C=N), 1582 (C=C), 1172 (C-Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.30-1.38 (t, 3H, J = 5.95 Hz, CH_3), 1.92-1.96 (d, 3H, J = 5.92 Hz, CH_3), 2.73 - 2.80 (t, 2H, J = 5.90 Hz, CH_2), 3.38 -3.45 (t, 2H, J = 5.89 Hz, CH_2), 4.50 (q, 1H, CH, J = 5.91 Hz, thiazole), 4.90-4.96 (q, 2H, J = 5.92 Hz, CH_2), 7.51-7.95 (m, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 19.1, 24.2 (2C, $2CH_3$), 29.7, 31.8, 37.2 (3C, $3CH_2$), 56.4 (1C, CH, thiazole), 128.5, 128.9,

132.8, 136.4, 152.5, 156.4 (8C, Ar-C), 172.3, 188.2 (2C, 2C=O); MS (70 eV): *m/z* = 351 (M^+, 98 %); Anal. Calc. (Found) for $C_{16}H_{18}ClN_3O_2S$ (351.85): C, 54.62 (54.54); H, 5.16 (5.24); N, 11.94 (11.85).

4.34. Synthesis of ***2-((4-benzoyl-5-oxotetrahydro-2H-thiopyran-2-ylidene) hydrazono)-3-substituted-5-methylthiazolidin-4-one*** **(11a-c)**

General Procedure: A mixture of **10a-c** (0.01 mol) mercaptoacetyl-chloride (1.10 g, 0.01 mol), and anhydrous potassium carbonate (2.08 g, 0.015 mol) in dry acetone (35 mL) was refluxed for 8-14h. The reaction mixture was allowed to cool to room temperature. Water (40 mL) was added and then the solid that separated was filtered off, dried and crystallized from the suitable solvent to give **11a-c**.

4.35. Synthesis of ***2-((4-benzoyl-5-oxotetrahydro-2H-thiopyran-2-ylidene) hydrazono)-5-methyl-3-phenylthiazolidin-4-one*** **(11a)**

The compound was obtained from the reaction of **10a** (3.99g, 0.01 mol) with mercaptoacetyl-chloride, as white crystals, crystallized from methanol in 82% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3052 (CH aryl), 2949 (CH alkyl), 1724, 1718, 1682, (3C=O), 1626 (C=N), 1584(C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.73-1.77 (d, 3H, *J* = 5.90 Hz, CH_3), 2.68-2.74 (d, 2H, *J* = 5.95 Hz, CH_2, thiopyran), 4.02 (d, 1H, *J* = 5.93 Hz, CH_2, thiopyran), 4.10 (d, 1H, *J* = 5.95 Hz, CH_2, thiopyran), 4.40 (q, 1H, *J* = 5.89 Hz, CH, thiazole), 5.95 (t, 1H, *J* = 5.91 Hz, CH, thiopyran), 7.40 -7.98 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 25.1 (1C, CH_3), 28.5, 35.7 (2C, $2CH_2$), 51.2, 58.4 (2C, 2CH), 127.3, 127.9, 128.4, 128.7, 129.1, 132.4, 134.7, 135.9, 155.5, 160.2 (14C, Ar-C), 173.6, 187.1, 195.5 (3C, 3C=O); MS (70 eV): *m/z* = 437 (M^+, 100%); Anal. Calc. (Found) for $C_{22}H_{19}N_3O_3S_2$ (437.53): C, 60.39 (60.47); H, 4.38 (4.30); N, 9.60 (9.70).

4.36. Synthesis of ***2-((4-benzoyl-5-oxotetrahydro-2H-thiopyran-2-ylidene) hydrazono)-3-benzyl-5-methylthiazolidin-4-one*** **(11b)**

The compound was obtained from the reaction of **10b** (4.13g, 0.01 mol) with mercaptoacetyl-chloride, as yellow crystals, crystallized from dioxane in 78% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3050 (CH aryl), 2947 (CH alkyl), 1725, 1720, 1685, (3C=O), 1622 (C=N), 1580 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.70 - 1.74 (d, 3H, *J* = 5.92 Hz, CH_3), 2.65-2.71 (d, 2H, *J* = 5.94 Hz,

CH_2, thiopyran), 4.05 (d, 1H, *J* = 5.96 Hz, CH_2, thiopyran), 4.12 (d, 1H, *J* = 5.97 Hz, CH_2, thiopyran), 4.43 (q, 1H, *J* = 5.90 Hz, CH, thiazole), 5.55 (s, 2H, CH_2), 5.90 (t, 1H, *J* = 5.94 Hz, CH, thiopyran), 7.30 -7.95 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 25.6 (1C, CH_3), 28.2, 35.4, 38.9 (3C, $3CH_2$), 51.5, 58.7 (2C, 2CH), 126.8, 127.4, 128.3, 128.5, 128.9, 132.7, 134.3, 135.6, 155.2, 160.7 (14C, Ar-C), 173.2, 186.9, 195.8 (3C, 3C=O); MS (70 eV): *m/z* = 451 (M^+, 90%); Anal. Calc. (Found) for $C_{23}H_{21}N_3O_3S_2$ (451.56): C, 61.18 (61.24); H, 4.69 (4.60); N, 9.31 (9.37).

4.37. Synthesis of ***2-((4-benzoyl-5-oxotetrahydro-2H-thiopyran-2-ylidene) hydrazono)-3-ethyl-5-methylthiazolidin-4-one*** **(11c)**

The compound was obtained from the reaction of **10c** (3.51g, 0.01 mol) with mercaptoacetyl-chloride, as yellowish crystals, crystallized from benzene in 80% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3055 (CH aryl), 2945 (CH alkyl), 1722, 1723, 1680, (3C=O), 1627 (C=N), 1586 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.25-1.33 (t, 3H, *J* = 5.93 Hz, CH_3), 1.66 - 1.70 (d, 3H, *J* = 5.97 Hz, CH_3), 2.75-2.81 (d, 2H, *J* = 5.90 Hz, CH_2, thiopyran), 4.09 (d, 1H, *J* = 5.92 Hz, CH_2, thiopyran), 4.17 (d, 1H, *J* = 5.94 Hz, CH_2, thiopyran), 4.47 (q, 1H, *J* = 5.96 Hz, CH, thiazole), 4.82- 4.88 (q, 2H, *J* = 5.95 Hz, CH_2), 5.99 (t, 1H, *J* = 5.98 Hz, CH, thiopyran), 7.58 -7.99 (m, 5H, Ar-H); ^{13}C NMR (DMSO-d_6) δ = 19.5, 25.9 (2C, $2CH_3$), 28.8, 35.1, 38.5 (3C, $3CH_2$), 51.7, 58.9 (2C, 2CH), 128.4, 128.8, 132.9, 135.7, 156.5, 161.2 (8C, Ar-C), 174.1, 187.3, 194.9 (3C, 3C=O); MS (70 eV): *m/z* = 389 (M^+, 95%); Anal. Calc. (Found) for $C_{18}H_{19}N_3O_3S_2$ (389.49): C, 55.51 (55.60); H, 4.92 (4.85); N, 10.79 (10.71).

4.38. Synthesis of ***N''-(3-substituted-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazon- hydrazide*** **(12a-c)**

General Procedure: A mixture of **10a-c** (0.01 mol), and hydrazine hydrate (99-100 %, 10 mL) was stirred under reflux in dioxane (35 mL) and ethanol (5 mL) for 10-15h. The reaction mixture was allowed to cool to zero ℃ for 6 h, and the solid was collected by filtration and crystallized from the appropriate solvent to give **12a-c**.

4.39. Synthesis of ***N''-(5-methyl-4-oxo-3-phenylthiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazonhydrazide*** **(12a)**

The compound was obtained from the reaction of **10a** (3.99g, 0.01 mol) with hydrazine hydrate, as a pale yellow crystals, crystallized from dioxane in 91% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3430-3355 (br s, NH-NH_2), 3045 (CH aryl), 2940 (CH alkyl), 1732, 1688, (2C=O), 1630 (C=N), 1578(C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.75- 1.79 (d, 3H, J = 5.95 Hz, CH_3), 2.74- 2.80 (t, 2 H, J = 5.91 Hz, CH_2), 3.28-3.35 (t, 2H, J = 5.90 Hz, CH_2), 4.49 (q, 1H, J = 5.95 Hz, CH, thiazole), 6.60 (br, NH_2, D_2O exchangeable), 7.38 -7.97 (m, 10H, Ar-H), 10.50 (br, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 24.9 (1C, CH_3), 29.7, 33.5 (2C, $2CH_2$), 56.8 (1C, CH, thiazole), 127.6, 128.2, 128.4, 128.6, 128.8, 132.7, 135.6, 136.5, 155.7, 159.4 (14C, Ar-C), 171.5, 184.8 (2C, 2C=O); MS (70 eV): m/z = 395 (M^+, 100%); Anal. Calc. (Found) for $C_{20}H_{21}N_5O_2S$ (395.48): C, 60.74 (60.82); H, 5.35 (5.28); N, 17.71 (17.64).

4.40. Synthesis of ***N''-(3-benzyl-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazonhydrazide*** **(12b)**

The compound was obtained from the reaction of **10b** (4.13g, 0.01 mol) with hydrazine hydrate, as yellow crystals, crystallized from DMF in 84% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3435-3358 (br s, NH-NH_2), 3049 (CH aryl), 2945 (CH alkyl), 1733, 1690, (2C=O), 1632 (C=N), 1580 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.78 - 1.82 (d, 3H, J = 5.93 Hz, CH_3), 2.77 - 2.83 (t, 2H, J = 5.96 Hz, CH_2), 3.31 -3.38 (t, 2H, J = 5.97 Hz, CH_2), 4.51 (q, 1H, J = 5.92 Hz, CH, thiazole), 5.60 (s, 2H, CH_2), 6.70 (br, NH_2, D_2O exchangeable), 7.32 -7.94 (m, 10H, Ar-H), 10.60 (br, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 25.3 (1C, CH_3), 28.2, 32.4, 38.5 (3C, $3CH_2$), 56.3 (1C, CH, thiazole), 127.1, 127.5, 128.2, 128.5, 128.7, 132.9, 135.8, 136.8, 155.9, 159.7 (14C, Ar-C), 170.8, 183.9 (2C, 2C=O); MS (70 eV): m/z = 409 (M^+, 98%); Anal. Calc. (Found) for $C_{21}H_{23}N_5O_2S$ (409.51): C, 61.59 (61.50); H, 5.66 (5.71); N, 17.10 (17.03).

4.41. Synthesis of ***N''-(3-ethyl-5-methyl-4-oxothiazolidin-2-ylidene)-4-oxo-4-phenylbutane hydrazonhydrazide*** **(12c)**

The compound was obtained from the reaction of **10c** (3.51g, 0.01 mol) with hydrazine hydrate, as yellowish crystals, crystallized from ethanol in 87% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3440-3350 (br s, NH-NH_2), 3052 (CH aryl), 2950 (CH alkyl), 1735, 1692, (2C=O), 1634 (C=N), 1582 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.28-1.36 (t, 3H, J = 5.98 Hz, CH_3), 1.81 - 1.85 (d, 3H, J = 5.97 Hz, CH_3), 2.80 - 2.86 (t, 2H, J = 5.94 Hz, CH_2), 3.33 -3.40 (t, 2H, J = 5.91 Hz, CH_2),

4.55 (q, 1H, *J* = 5.93 Hz, CH, thiazole), 4.93 - 4.99 (q, 2H, *J* = 5.94 Hz, CH_2), 6.80 (br, NH_2, D_2O exchangeable), 7.55 -7.96 (m, 5H, Ar-H), 10.72 (br, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 20.1, 26.3 (2C, $2CH_3$), 28.6, 32.7, 39.1 (3C, $3CH_2$), 56.8 (1C, CH, thiazole), 128.4, 128.9, 133.3, 136.2, 156.1, 158.8 (8C, Ar-C), 170.5, 183.7 (2C, 2C=O); MS (70 eV): *m/z* = 347 (M^+, 99 %); Anal. Calc. (Found) for $C_{16}H_{21}N_5O_2S$ (347.44): C, 55.31 (55.40); H, 6.09 (6.01); N, 20.16 (20.24).

4.42. Synthesis of ***3-substituted-5-methyl-2-((6-phenyl - 4, 5-dihydropyridazin-3(2H)-ylidene) hydrazono) thiazolidin-4-one*** **(13a-c)**

General Procedure: The compounds **12a-c** (0.01 mol), was refluxed in dimethylformamide (45 mL) and anhydrous potassium carbonate (2.08g, 0.015 mol) for 15-18h (under TLC control). The reaction was cooled; the deposited precipitate was filtered off, washed with ethanol and dried, and crystallized from appropriate solvent to produce **13a-c** in good yield.

4.43. Synthesis of ***5-methyl-3-phenyl-2-((6-phenyl-4, 5-dihydropyridazin-3(2H)-ylidene) hydrazono) thiazolidin-4-one*** **(13a)**

The compound was obtained from the reaction of **12a** (3.95g, 0.01 mol) with DMF, as yellow crystals, crystallized from benzene in 79% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3340 (br. s, NH), 3070 (CH aryl), 2960 (CH alkyl), 1682, (C=O), 1636 (C=N), 1583(C=C) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.72- 1.76 (d, 3H, *J* = 6.01 Hz, CH_3), 2.10 - 2.18 (t, 2H, *J* = 6.04 Hz, CH_2), 2.20 -2.27 (t, 2H, *J* = 6.03 Hz, CH_2), 4.53 (q, 1H, *J* = 6.05 Hz, CH, thiazole), 7.22 -7.65 (m, 10H, Ar-H), 11.30 (br, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 24.5(1C, CH_3), 26.1, 28.4 (2C, $2CH_2$), 55.7 (1C, CH, thiazole), 127.1, 127.5, 127.8, 128.2, 128.5, 128.7, 134.9, 137.4, 144.7, 157.3, 159.8 (15C, Ar-C), 174.7 (1C, C=O); MS (70 eV): *m/z* = 377 (M^+, 90%); Anal. Calc. (Found) for $C_{20}H_{19}N_5OS$ (377.47): C, 63.64 (63.55); H, 5.07 (5.13); N, 18.55 (18.62).

4.44. Synthesis of ***3-benzyl-5-methyl-2-((6-phenyl-4, 5-dihydropyridazin-3(2H)-ylidene) hydrazono) thiazolidin-4-one*** **(13b)**

The compound was obtained from the reaction of **12b** (4.09g, 0.01 mol) with DMF, as yellowish crystals, crystallized from toluene in 72% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3345 (br. s, NH), 3072 (CH aryl), 2963 (CH alkyl), 1684 (C=O), 1632 (C=N), 1581(C=C) cm^{-1}; ^1H NMR

(DMSO-d_6): δ = 1.74 - 1.78 (d, 3H, J = 6.07Hz, CH_3), 2.13 - 2.21 (t, 2 H, J = 6.06 Hz, CH_2), 2.24 -2.31 (t, 2H, J = 6.08 Hz, CH_2), 4.58 (q, 1H, J = 6.09 Hz, CH, thiazole), 5.52 (s, 2H, CH_2), 7.20-7.63 (m, 10H, Ar-H), 11.25 (br, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 24.8(1C, CH_3), 26.5, 28.7, 39.4 (3C, $3CH_2$), 55.9 (1C, CH, thiazole), 127.3, 127.7, 127.9, 128.4, 128.7, 128.9, 135.1, 138.2, 144.5, 157.8, 160.2 (15C, Ar-C), 175.1 (1C, C=O); MS (70 eV): *m/z* = 391 (M^+, 86%); Anal. Calc. (Found) for $C_{21}H_{21}N_5OS$ (391.49): C, 64.43 (64.34); H, 5.41 (5.35); N, 17.89 (17.95).

4.45. Synthesis of ***3-ethyl-5-methyl-2-((6-phenyl-4, 5-dihydropyridazin-3(2H)-ylidene) hydrazono) thiazolidin-4-one*** **(13c)**

The compound was obtained from the reaction of **12c** (3.47g, 0.01 mol) with DMF, as white crystals, crystallized from dioxane in 76% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3348 (br. s, NH), 3075 (CH aryl), 2966 (CH alkyl), 1688 (C=O), 1635 (C=N), 1584(C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.22-1.30 (t, 3H, J = 6.01 Hz, CH_3), 1.79 - 1.83 (d, 3H, J = 6.03 Hz, CH_3), 2.12 - 2.20 (t, 2H, J = 6.04 Hz, CH_2), 2.28 -2.35 (t, 2H, J = 6.02 Hz, CH_2), 4.60 (q, 1H, J = 6.08 Hz, CH, thiazole), 4.85- 4.92 (q, 2H, J = 6.05 Hz, CH_2), 7.25-7.40 (m, 5H, Ar-H), 11.20 (br, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) δ = 21.2, 26.7 (2C, $2CH_3$), 28.9, 33.1, 39.5 (3C, $3CH_2$), 56.2 (1C, CH, thiazole), 127.4, 128.3, 128.6, 136.8, 144.3, 155.7, 159.1 (9C, Ar-C), 173.4 (1C, C=O); MS (70 eV): *m/z* = 329 (M^+, 94%); Anal. Calc. (Found) for $C_{16}H_{19}N_5OS$ (329.42): C, 58.34 (58.26); H, 5.81 (5.74); N, 21.26 (21.33).

4.46. Synthesis of ***1-((3-substituted-5-methyl-4-oxothiazolidin-2-ylidene) amino)-6-chloro-5-phenyl-3, 4-dihydro-1H-azepine-2, 7-dione*** **(14a-c)**

General Procedure: A mixture of **9a-c** (0.01mol) and chloro-acetyl-chloride (1.12 g, 0.01mol) was refluxed in ethanol (50 mL) in the presence of potassium hydroxide (0.01mol) for 16-19h. The reaction mixture was cooled with water; the deposited precipitate was filtered off, washed with ethanol, dried, and crystallized from the suitable solvent to afford **14a-c**.

4.47. Synthesis of ***6-chloro-1-((5-methyl-4-oxo-3-phenylthiazolidin-2-ylidene) amino)-5-phenyl-3, 4-dihydro-1H-azepine-2, 7-dione*** **(14a)**

The compound was obtained from the reaction of **9a** (3.81g, 0.01 mol) with chloro-acetyl chloride, as yellowish crystals, crystallized from dimethylformamide in 74% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3070 (CH aryl), 2960 (CH alkyl), 1690, 1685, 1680 (3C=O), 1630 (C=N), 1585 (C=C), 1185 (C-Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.69 (d, 3H, J = 6.10 Hz, CH_3), 2.02 - 2.22 (t, 2H, J = 6.12 Hz, CH_2), 2.27 -2.35 (t, 2H, J = 6.14 Hz, CH_2), 4.38 (q, 1H, CH, J = 6.13 Hz, thiazole), 7.06-7.92 (m, 10H, Ar-H). ^{13}C NMR (DMSO-d_6) δ = 21.3 (1C, CH_3), 23.3, 32.9 (2C, $2CH_2$), 61.8 (1C, CH, thiazole), 117.7 (1C,C-Cl), 123.9, 126.4, 129.9, 131.9, 132.5, 132.9, 135.4, 141.9, 148.9, 155.1 (14C, Ar-C), 161.3, 167.6, 168.1 (3C, 3C=O); MS (70 eV): *m/z* = 439 (M^+, 100 %); Anal. Calc. (Found) for $C_{22}H_{18}ClN_3O_3S$ (439.91): C, 60.07 (60.15); H, 4.12 (4.20); N, 9.55 (9.46).

4.48. Synthesis of ***1-((3-benzyl-5-methyl-4-oxothiazolidin-2-ylidene) amino)-6-chloro-5-phenyl-3, 4-dihydro-1H-azepine-2, 7-dione*** **(14b)**

The compound was obtained from the reaction of **9b** (3.95g, 0.01 mol) with chloro-acetyl chloride, as yellow crystals, crystallized from dioxane in 70% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3075 (CH aryl), 2965 (CH alkyl), 1693, 1688, 1682(3C=O), 1632 (C=N), 1587 (C=C), 1182 (C-Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.75 (d, 3H, J = 6.08 Hz, CH_3), 2.05- 2.25 (t, 2 H, J = 6.09 Hz, CH_2), 2.26 -2.34 (t, 2H, J = 6.07 Hz, CH_2), 4.40 (q, 1H, CH, J = 6.05 Hz, thiazole), 5.60 (s, 2H, CH_2), 7.05-7.90 (m, 10H, Ar-H).^{13}C NMR (DMSO-d_6) δ = 24.6 (1C, CH_3), 27.7, 30.8, 38.5 (3C, $3CH_2$), 58.5 (1C, CH, thiazole), 119.8 (1C,C-Cl), 126.5, 127.1, 127.4, 127.8, 128.4, 128.7, 135.8, 137.9, 150.7, 154.1 (14C, Ar-C), 162.2, 168.3, 169.4 (3C, 3C=O); MS (70 eV): *m/z* = 453 (M^+, 90%); Anal. Calc. (Found) for $C_{23}H_{20}ClN_3O_3S$ (453.94): C, 60.86 (60.94); H, 4.44 (4.51); N, 9.26 (9.16).

4.49. Synthesis of ***6-chloro-1-((3-ethyl-5-methyl-4-oxothiazolidin-2-ylidene) amino)-5-phenyl-3, 4-dihydro-1H-azepine-2, 7-dione*** **(14c)**

The compound was obtained from the reaction of **9c** (3.33g, 0.01 mol) with chloro-acetyl chloride, as yellowish crystals, crystallized from dimethylformamide in 73% yield, m. p. >350 °C. IR (KBr): ν_{max} = 3079 (CH aryl), 2968 (CH alkyl), 1695, 1690, 1684(3C=O), 1635 (C=N), 1590 (C=C), 1180 (C-Cl) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.27-1.35 (t, 3H, J = 6.04 Hz, CH_3), 1.80 (d, 3H, J = 6.02 Hz, CH_3), 2.08 - 2.27(t, 2H, J = 6.01 Hz, CH_2), 2.28 -2.37 (t, 2H, J = 6.06 Hz, CH_2),

4.45 (q, 1H, CH, J = 6.08 Hz, thiazole), 4.77- 4.84 (q, 2H, J = 6.03 Hz, CH_2), 7.02 -7.40 (m, 5H, Ar-H).^{13}C NMR (DMSO-d_6) δ = 20.5, 25.9 (2C, $2CH_3$), 27.8, 32.9, 38.7 (3C, $3CH_2$), 58.9 (1C, CH, thiazole), 119.5 (1C,C-Cl), 126.8, 128.1, 128.8, 138.4, 151.2, 154.5 (8C, Ar-C), 162.6, 166.5, 170.1 (3C, 3C=O); MS (70 eV): *m/z* = 391 (M^+, 95%); Anal. Calc. (Found) for $C_{18}H_{18}ClN_3O_3S$ (391.87): C, 55.17 (55.25); H, 4.63 (4.70); N, 10.72 (10.64).

4.50. ***MATERIAL AND METHODS***

4.51. ***Biological screening***

The antimicrobial activity of the newly prepared compounds was tested *in vitro* against Gram-positive bacteria *Streptococcus pyogenes, Staphylococcus aureus*, Gram-negative bacteria *Klebsiella pneumoniae, Escherichia coli,* and the fungi *Candida albicans, Curvularia lunata, Alternaria alternate* and *Aspergillus niger***.** The newly prepared compounds were dissolved in dimethyl sulfoxide (DMSO) and tested for their antimicrobial activity by the agar disk diffusion technique. Cefotaxime sodium and nystatin, [1-3, 21, 36, 49] were used as the standard drugs for antibacterial and antifungal assays, respectively. A solution of 100 μg mL^{-1} of the tested compound was practical and microplate-wells, 1 cm in diameter, were used. Zones of inhibition were measured with calipers or automated scanners and were paralleled with those of the standards. Cefotaxime sodium (0.15μmol mL^{-1}) and nystatin (0.037 μmol mL^{-1}) were used as the standard drugs for antibacterial and antifungal activity, respectively. Compound-impregnated disks were placed on an agar plate containing a standard suspension of microorganisms. The plate was incubated for 24 h at 37 °C. For the assessment of the minimum inhibitory concentration (MIC) by the serial plate dilution way, [1-3, 21, 36, 49] 5 mg of each tested compound was dissolved in 1 mL of DMSO separately to prepare stock solutions. Serial dilutions were prepared from each stock solution. The plates were incubated at 37 °C for 24 h. MIC is defined as the lowest concentration (μmol mL^{-1}) of the tested compound that results in no visible growth on the plates. DMSO was used as the solvent control to ensure that the solvent had no effect on bacterial growth. Notice: This experiment was repeated three times on the same prepared compounds and the ideal drugs according to the same conditions with calculation an average of the minimum inhibitory concentration (MIC).The results are shown in Tables **1** and **2**.

5. CONCLUSION

Many of the newly prepared compounds in this article possess a broad antimicrobial activity and these heterocyclic organic compounds contain many functional groups as effective antimicrobials, these compounds were obtained in good yields *via* using new procedures that provide rapid and efficient, these compounds include ethyl 4-oxo-phenylbutanoate (**2**), phenyl -butanehydrazide (**3**), *N*-substituted-2-(4-oxo-phenylbutanoyl) hydrazine-carbothioamide (**4a-c**), substituted-1, 2, 4-triazole (**5a-c**), substituted-1, 3, 4-oxadiazole (**6a-c**), substituted-1, 3, 4-thiadiazole (**7a-c**), *N'*-(substituted-oxothiazolidine) phenylbutanehydrazide (**8a-c**), *N'*-(substituted-oxothiazolidine)-4-phenylbutane-hydrazide (**9a-c**), *N*-(substituted-oxothiazolidine)-hydrazonoyl-chloride (**10a-c**), (thiopyrane) hydrazono-substituted-thiazolidinone (**11a-c**), *N''*-(substituted-oxothiazolidine)-phenylbutane-hydrazon-hydrazide (**12a-c**), substituted-(pyridazine) hydrazono-thiazolidinone (**13a-c**), (substituted-oxothiazolidine) azepine-2,7-dione (**14a-c**). Moreover, the best compounds that give effective antimicrobial activity are pyridazin-hydrazono-thiazolidinone (**13a-c**), oxothiazolidine-azepine-dione (**14a-c**), *N*-oxothiazolidine-hydrazon-hydrazide (**12a-c**) and thiopyrane-hydrazono-thiazolidinone (**11a-c**), because these compounds are containing pyridazine, thiazolidinone, azepine and thiopyran ring with several functional groups as phenyl, benzoyl, ethyl, methyl, chloro, thioxo, carbonyl and amino group when compared to the standard drugs (cefotaxime sodium and nystatin).

Ethics Approval and Consent to Participate

All the procedures adopted were approved and agreed upon by the Animal Ethical Committee of the National Research Centre, Department of Chemistry of Natural and Microbial Products, Giza12622, Egypt.

Human and Animal Rights

No humans or animals were used in the study. The research was conducted in accordance with ethical standards.

CONSENT FOR PUBLICATION

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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