Synthesis and evaluation of antimicrobial activity of some new heterocyclic compounds using succinic acid dihydrazide as a precursor

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Abstract—Utility of succinic acid dihydrazide for the synthesis of some new heterocyclic compounds, containing bis-1,3,4-oxadiazole, bis-4-thiazolidinone, bis-5-amino-3-pyrazolone and bis-1,3-dioxo-isoindole. The chemical structures of the prepared compounds have been confirmed by their elemental analysis, FT-IR, 1H NMR and Mass spectra. Investigation of the antimicrobial activity of the compounds was done by the paper disc technique. Some of the tested compounds showed the most favorable antimicrobial activity.

Index Terms— Antimicrobial activity, 1,3,4-oxadiazole, succinic dihydrazide, 4-thiazolidinone, 1,3-dioxo-isoinde.

1 INTRODUCTION

It was observed from the literature that certain five membered heterocyclic compounds possess interesting biological activity. Among them the compounds bearing pyrazole and 1,3,4-oxadiazole nucleus which have wide applications in medicinal chemistry. These compounds also have been reported to have significant antitubercular activity.[1-6] Screening the literature reveals that thiazolidinones exhibit also antinociceptive, [7] anti-inflammatory, [8] anti-toxoplasma gondii, [9] anticancer and HIV-1 RT inhibitor, [10] and antibacterial activites. [11-15]

Due to the highly observed biological activities of such compounds, a programme was set up to synthesize new derivatives of bis-1,3,4-oxadiazole, bis-4-thiazolidinone, bis-5-amino-3-pyrazolone and bis-1,3-dioxo-isoindole, where the linker moiety was an aliphatic hydrocarbon chain [-$(CH_2)_2$-], butane-1,4-diones [-CO-$(CH_2)_2$-CO-] or succinamide [-NH-CO-$(CH_2)_2$-CO-NH-], aims to investigate their antimicrobial activities.

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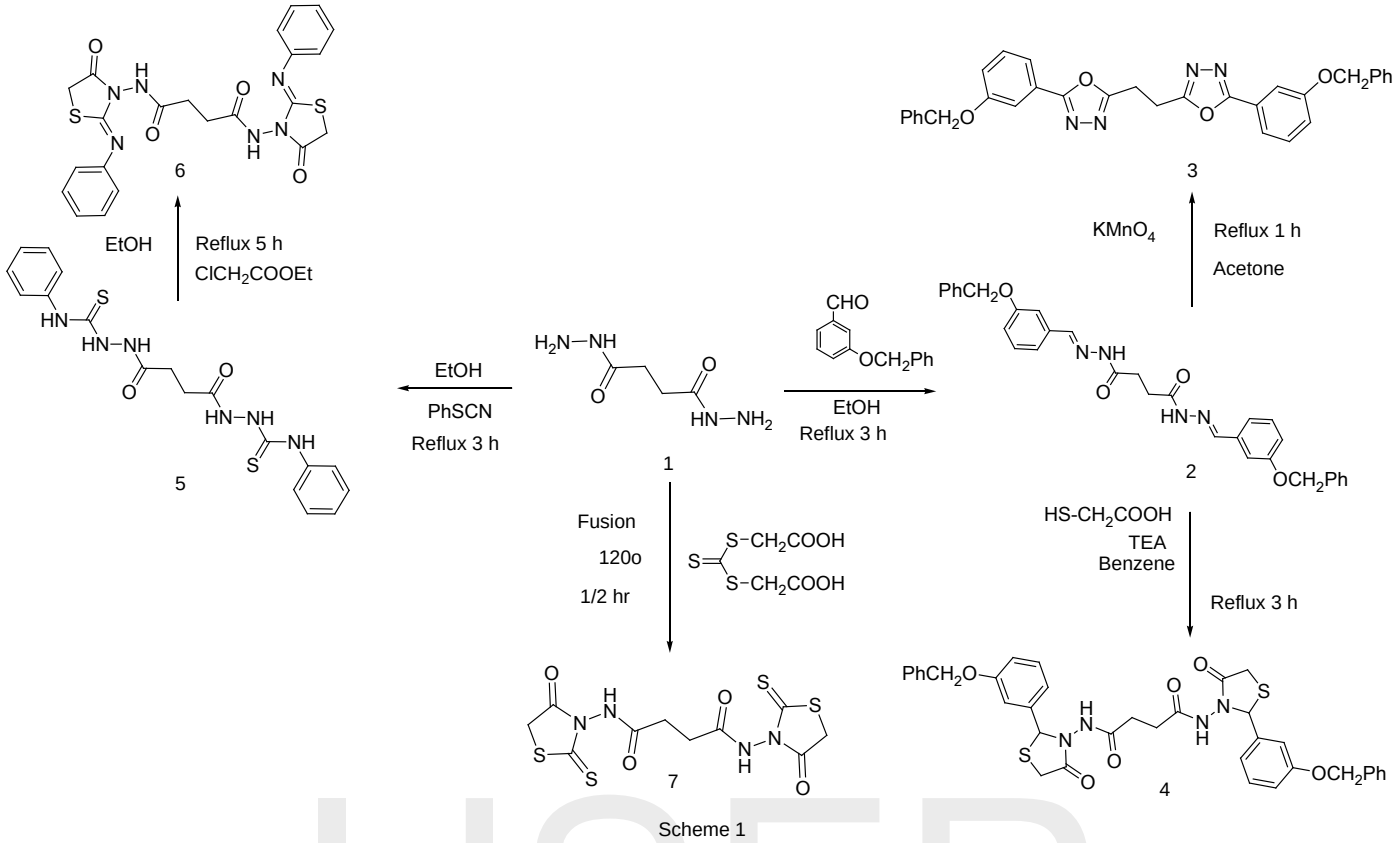
2 RESULTS AND DISCUSSION

Succinic acid dihydrazide (**1**) was prepared according to a reported method [16-18] by treatment of hydrazine hydrate with diethyl succinate. However, condensation of compound 1 with 3-benzloxy-benzaldehyde in refluxing ethanol afforded the corresponding hydrazone **2**, which on treatment of it with potassium permanganate in acetone, the corresponding 1,2-Bis-[5-(3-benzyloxy-phenyl)-1,3,4-oxadiazolyl]-ethane (**3**) was famed via intramolecular ring closer (Scheme 1). The chemical structure of the latter was elucidated through its spectral data. Thus, the ^{1}H NMR spectrum of **3** showed the absence of two singlets at 11.2 and 7.9 ppm corresponding to the NH and the (-CH=N-) protons, respectively (**Tables 1 & 2**). On the other hand, refluxing of compound **2** with thioglycolic acid in benzene in presence of triethyl amine afforded the corresponding *N,N'*-Bis-[2-(3-benzyloxy-phenyl)-4-oxo-thiazolidin-3-yl]-succinamide (**4**).

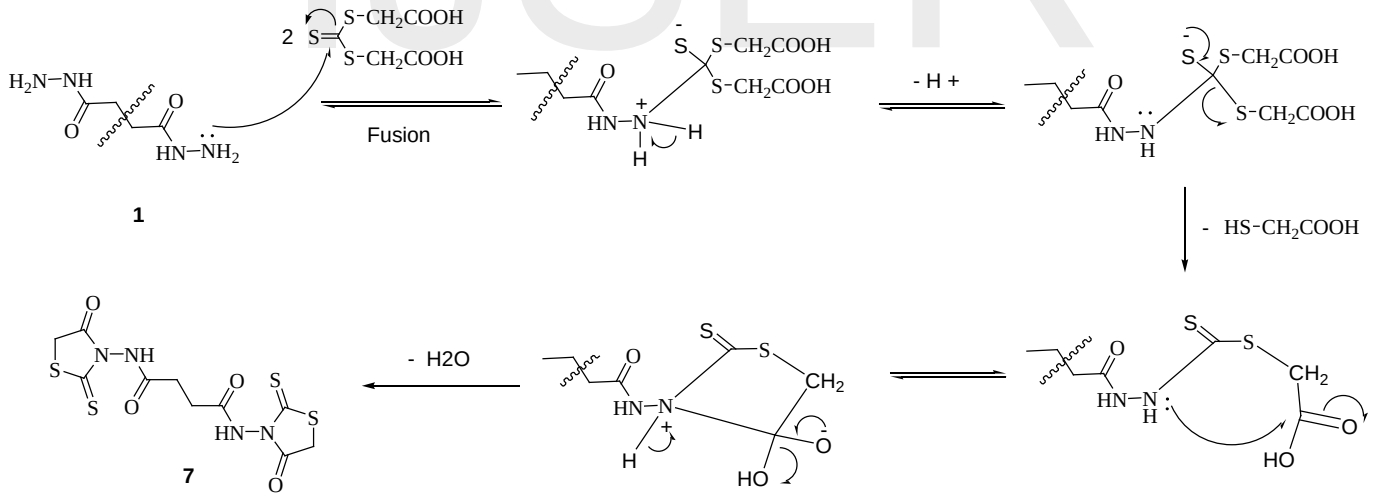
Compound **1** was reacted with phenyl isothiocyanate to give bis-(*N*-phenylhydrazine-carbothioamide) derivative **5,** which upon heating in ethanol, the corresponding bis-4-thiazolidinone derivative **6** was formed (**Scheme 1**). The elemental analyses and spectroscopic data are in consistent with the assigned structures of **4**, **5** and **6** (**Tables 1& 2**).

A new derivative of bis-4-thiazolidinone assigned as *N,N'*-Bis-(4-oxo-2-thioxo-thiazolidin-3-yl)-succinamide (**7**) was also prepared by fusion of the dihydrazide **1** with thiocarbonyl-bis-thioglycolic acid. The conversion of compound **1** to compound **7** may proceed *via* elimination of thioglycolic acid moiety followed by cyclic condensation through losing of water according to the proposed mechanism (**Scheme 2**). The structure of compound **7** was in agreement with its spectral data and elemental analysis as shown in (**Tables 1& 2**).



Scheme 1

Scheme 1. Synthesis of new bis-1,3,4-oxadiazole derivative **3** and bis-4-thiazolidinone derivatives **4, 6** and **7** from succinic dihyrazide **1**.



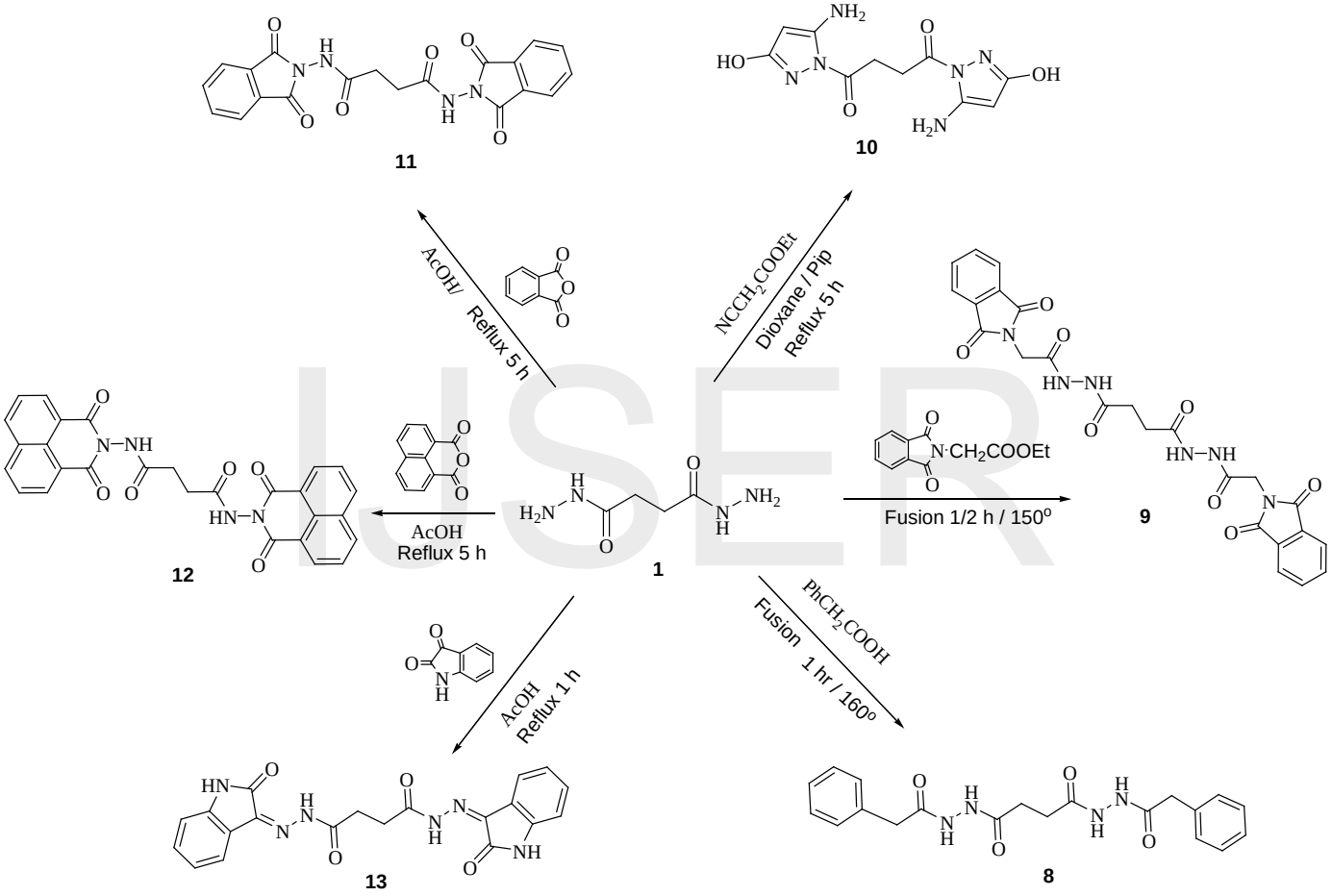
Scheme 2

Scheme 2. The suggested reaction mechanism of **1** to give bis-4-thiazolidinone derivative **7.**

Fusion of the dihydrazide **1** with phenyl acetic acid and ethyl *N*-phthaloylglycine afforded the corresponding diphenylacetyl-hydrazino-hydrazide derivative **8**, and bis-1,3-dioxo-isoindole derivative **9** respectively (**Scheme 3**). Mass spectra of compounds **8** and **9** showed ion peaks at *m*/*z* 382 and *m*/*z* 520, respectively, which were in agreement with assigned structures (**Tables 1& 2**).

A bis-5-amino-3-pyrazolone derivative **10** was obtained from condensation of succinic dihydrazide **1** with ethyl cyanoacetate in dioxane in the presence of pipredine as a catalyst (**Scheme 3**). IR spectrum of compound **10** showed absorption bands at 3400 for (OH), 3235 (NH_2), 2990- 2869 (CH_2) and 1672 cm^{-1} (C=O) groups. The ^1H NMR spectrum of **10** showed signals at 6.8 (s, 2H, 2OH), 5.8 (s, 2H, -CH=), 3.9 (s, 4H, $2NH_2$) and 2.48 (s, 4H, $2CH_2$). Mass spectrum showed molecular ion peak ($C_{10}H_{12}N_6O_4$) at *m*/*z* 280.

Boiling of comound **1** with phthalic anhydride and 1,8-naphthalic anhydride in glacial acetic acid afforded the corresponding bis-1,3-dioxo-isoindole derivative **11** and bis-1,3-dioxo-isoquinolin derivative **12**, respectively (**Scheme 3**). Furthermore condensation of the hydrazide **1** with isatin in refluxing acetic acid gave a product which assigned as *N,N'*-Bis-(3-imino-1,3-dihydro-indolyl-2-one)-succinamide **(13)** in good yield (80.4%). The chemical structure of compounds **11**, **12** and **13** were assigned on the bases of their spectral and elemental data (**Tables 1& 2**).



Scheme 3

Scheme 3. Condensation of succinic dihydrazide **1** with phenylacetic acid, ethyl *N*-phthaloylglycine, anhydrides and isatin.

Table 1: Yield, physical data and elemental analyses of the synthesized compounds 2- 13.

Comp. No.	Crystallization Solvent	m.p. (°C)	Yield (%)	Mol formula/ mol wt	Elemental Analysis				
						C %	H %	N %	S %
2	Dioxane	192- 194	87.4	$C_{32}H_{30}N_4O_4$ 534.61	Calc. Found	71.89 71.65	5.66 5.72	10.48 10.66	
3	Acetone	118- 120	68.3	$C_{32}H_{26}N_4O_4$ 530.57	Calc. Found	72.44 72.13	4.94 4.97	10.56 10.84	
4	Ethanol	130- 132	57.6	$C_{36}H_{34}N_4O_6S_2$ 682.81	Calc. Found	36.32 36.47	5.02 5.10	8.21 8.15	9.39 9.22
5	Dioxane	198- 200	86.2	$C_{18}H_{20}N_6O_2S_2$ 416.52	Calc. Found	51.90 51.81	4.84 4.69	20.18 20.44	15.40 15.38
6	Ethanol	238- 240	79.8	$C_{22}H_{20}N_6O_4S_2$ 496.56	Calc. Found	53.21 53.33	4.06 4.00	16.92 16.91	12.91 12.86
7	Ethanol	234- 236	66.1	$C_{10}H_{10}N_4O_4S_4$ 378.47	Calc. Found	31.71 31.66	2.66 2.57	14.80 14.92	33.89 33.91
8	Dioxane	230- 232	91.5	$C_{20}H_{22}N_4O_4$ 382.41	Calc. Found	62.82 62.78	5.80 5.83	14.65 14.66	
9	Acetic acid	310- 312	88.8	$C_{24}H_{20}N_6O_8$ 520.45	Calc. Found	55.39 55.48	3.87 3.81	16.15 16.12	
10	Ethanol	226- 228	92.3	$C_{10}H_{12}N_6O_4$ 280.24	Calc. Found	42.86 42.69	4.32 4.40	29.99 30.08	
11	Acetic acid/ H_2O	>360	89.1	$C_{20}H_{14}N_4O_6$ 406.35	Calc. Found	59.12 59.20	3.47 3.36	13.79 13.82	
12	Acetic acid/ H_2O	276- 278	85.6	$C_{28}H_{18}N_4O_6$ 506.47	Calc. Found	66.40 66.46	3.58 3.48	11.06 11.10	
13	Ethanol	240- 242	80.4	$C_{20}H_{16}N_6O_4$ 404.38	Calc. Found	59.40 59.39	3.99 3.90	20.78 20.88	

Table 2: Spectral data of compounds 2- 13.

Comp. No.	FT-IR (KBr) cm^{-1}	^1H NMR (DMSO-d_6) (δ ppm)	MS (m/z)
2	3212 (NH), 3066 (CH-aromatic), 2891 (CH_2), 1659 (C=O), 1618 (C=N).	11.2 (s, 2H, 2NH), 7.95 (s, 2H, 2 CH=N), 7.4-7.2 (m, 18H, arom-H), 5.13 (s, 4H, 2CH_2-O), 2.48 (t, 4H, 2CH_2).	534 ($M^{+\cdot}$), 500, 235, 146.
3	3041 (CH-aromatic), 2944- 2870 (CH_2), 1620 (C=N).	7.5-7.2 (m, 18H, arom-H), 5.15 (s, 4H, 2CH_2-O), 2.8 (t, 4H, 2CH_2).	530 ($M^{+\cdot}$), 249, 212, 91.
4	3228 (NH), 3078 (CH-aromatic), 2934- 2875 (CH_2), 1645(C=O).	8.7 (s, 2H, 2NH), 7.5-7.2 (m, 18H, arom-H), 5.9 (s, 2H, 2CH-S), 5.15 (s, 4H, 2CH_2-O), 3.2 (s, 4H, 2$COCH_2$-S), 2.49 (t, 4H, 2CH_2)	682 ($M^{+\cdot}$), 511, 420, 330.
5	3230, 3200 (NH's), 3007(CH-aromatic), 2940 (CH_2), 1698 (C=O).	10.18 (s, 2H, 2NH-CO), 9.82 (s, 2H, 2PhNHCS), 9.76 (s, 2H, 2NHCS), 7.56-6.95 (m, 10H, arom-H), 2.5 (t, 4H, 2CH_2).	416 ($M^{+\cdot}$), 280, 250, 144
6	3228 (NH), 3126 (CH arom.), 3028 (CH_2),	9.8 (s, 2H, 2NH), 7.6-6.9 (m, 10H, arom-H), 3.1 (s, 4H, 2$COCH_2$-S), 2.5 (t, 4H, 2CH_2).	496 ($M^{+\cdot}$), 476, 414, 341.

	1660(C=O).		
7	3216 (NH), 3015-2831(CH_2), 1710, 1698 (C=O).	11.0 (s, 2H, 2NH), 4.4 (s, 4H, 2$COCH_2$-S), 2.49 (t, 4H, 2CH_2).	378 ($M^{+\cdot}$), 304, 231, 157.
8	3199 (NH), 3030 (CH-aromatic), 2896 (CH_2), 1650 (C=O).	10.0 (s, 4H, 4NH), 7.4-6.9 (m, 10H, arom-H), 3.4 (s, 4H, 2CH_2-Ph), 2.51 (t, 4H, 2CH_2).	382 ($M^{+\cdot}$), 368, 313, 262.
9	3225 (NH), 3014(CH-aromatic), 2892 (CH_2), 1661 (C=O).	11.5 (s, 4H, 4NH), 8.0-7.8 (m, 8H, arom-H), 3.39 (s, 4H, 2CH_2-N), 2.49 (t, 4H, 2CH_2).	520 ($M^{+\cdot}$), 496, 402 162.
10	Broad band at 3400 (OH), 3235 (NH_2), 2980- 2869 (CH, CH_2), 1672 (C=O).	6.8 (s, 2H, 2OH), 5.8 (s, 2H, -CH=), 3.9 (s, 4H, 2NH_2), 2.48 (s, 4H, 2CH_2).	280 ($M^{+\cdot}$), 258, 218, 114.
11	3277 (NH), 2997 (CH-aromatic), 2886 (CH_2), 1800, 1750, 1671 (C=O).	10.7 (s, 2H, 2NH), 8.1-7.9 (m, 8H, arom-H), 2.5 (t, 4H, 2CH_2).	406 ($M^{+\cdot}$), 292, 246, 128.
12	3265 (NH), 3066 (CH-aromatic), 2869 (CH_2), 1771- 1738, 1669 (C=O).	10.8 (s, 2H, 2NH), 8.5-7.8 (m, 12H, arom-H), 2.49 (t, 4H, 2CH_2).	506 ($M^{+\cdot}$), 475, 347, 220.
13	3216 (NH), 2980 (CH-aromatic), 2876 (CH_2), 1683 (C=O), 1615 (C=N).	12.4 (s, 2H, indole-NH), 11.2 (s, 2H, amidic NH), 7.5-6.9 (m, 8H, arom-H), 2.49 (t, 4H, 2CH_2).	404 ($M^{+\cdot}$), 368, 272, 145.

ANTIMICROBIAL ACTIVITY

Bacterial source and culture condition:

The used Bacterial strains were Gram negative bacteria including *Pseudomonas aeruginosa* (ATCC 278223) and Gram positive bacteria (Methicillin-Resistant *Staphylococcus aureus* MRSA (ATCC 43300), and the fungus *Aspergillus Niger* that was isolated from an infected plant.

Culture media:

a- Mueller-Hinton agar (MHA, g l^{-1}) for bacteria [19]: Beef extract, 3.0; Peptone, 17.5; Starch, 1.5; Agar, 17, pH= 7.3 ± 0.1. Theplates were incubated at 37ºC for 24 – 48 hrs.

b- Czapek's medium for fungi (gl^{-1}): Sodium nitrate, 2.0; potassium dihydrogen phosphate, 1.0; magnesium sulfate, 0.5; potassium chloride, 0.5; ferrous sulfate, 0.01; glucose, 10; agar, 15. Chloramphenicol (0.05 mg/ml) was used as bacteriostatic agent. [20] The plates were incubated at 28 ºC for 5- 7 days.

Antimicrobial Test: The antimicrobial activities of samples were determined by filter paper disc method as described by Omenka & Osuoha. [21]

Paper disc technique: Antibacterial activity was determined against the above strains using the paper disc assay method (Bauer et al [22]. Whatman number 1 filter paper disc of 7.0 mm diameter was sterilized by autoclaving for 20 min at 121 °C. The sterile discs were impregnated with the different extracts (50 mg ml^{-1}). Agar plates were surface inoculated uniformly from the broth culture of the tested microorganism. In all cases, the concentration was approximately $1.5X10^8$ CFU ml^{-1}. The impregnated discs were placed on the Muller Hinton medium suitably spaced apart and the plates were incubated at 37°C for 48 h. Chloramphenicol-treated strains were used as a positive control. Diameter of the growth inhibition halos caused by samples were measured and expressed in millimeter. All the assays were carried out in triplicate.

Table 3: Effect of the synthesized compounds (2- 13) on growth (mm) of bacterial and fungal species.

Comp.	Gram (+ve) Bacteria	Gram (-ve) Bacteria	Fungi

No.	MRSA	*Pseudomon asaeruginosa*	*Aspergillus Niger*
2	6	10	----
3	6	9	----
4	6	6	----
5	----	----	----
6	----	9	----
7	6	7	----
8	----	7	----
9	6	8	----
10	----	8	----
11	6	7	----
12	6	17	----
13	6	7	----
control	32.5	21.5	----

Bacterial infection causes high rate of mortality in human population and aquaculture organisms.[23] For example, *Staphylococcus aureus* and *Pseudomonas aeruginosa* cause diseases like mastitis, abortion and upper respiratory complications.[24] *P. Aeruginosa* is an important and prevalent pathogen among burned patients capable of causing life-threatening illness.[23] *A. Niger* is one of the most common causes of otomycosis (fungal ear infections), which can cause pain, temporary hearing loss, and, in severe cases, damage to the ear canal and tympanic membrane.

The study deals with antibacterial and antifungal activity of different chemical compounds, the antibacterial activity of the synthesized compounds **2- 13** were carried out on the growth of two pathogenic bacteria (Methicillin-Resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*), while the antifungal activity of these compounds were done on the growth of *Aspergillus niger*. The inoculated plates by pathogenic bacteria were incubated at 37°C for 1-2 days and inhibition zones were measured.

The data obtained in Table (**3**) indicate that, the effect of these compounds was clear on *Pseudomonas aeruginosa* where 12/13 compounds were effected, the greater inhibition was observed by bis-1,3-dioxo-isoquinolin derivative **12** (17 mm), but the lowest inhibition was appeared by compound **4** (6 mm). The hydrazone **2**, oxadiazole **3** and thiazolidinone **6** showed high inhibition (8- 10 mm), while the carbothioamide derivative **5** showed no activity.

The inhibition effect was decreased on MRSA 9/13 and the tested compounds showed moderate inhibition effect (6 mm). Also, It can be seen from Table (**3**) that, all the synthesized compounds **2-13** had no effect against fungi (*Aspergillus niger)*, where several investigations have been carried out of antibacterial activities, but few have been recognized for many decades on their antifungal activities. [25]

3 EXPERIMENTAL PART

Melting points (uncorrected) were recorded on an Electrothermal melting apparatus. The IR spectra were recorded on a Shimadzu FT-IR 8101 PC spectrometer. The ^{1}H NMR spectra were determined in DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer; Chemical shifts are reported in ppm with TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a GCMS-QP 1000 EX spectrometer. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Synthesis of *N,N′*-Bis{(E)-[3-(benzyloxy)phenyl]methylene} succinohydrazide (2). A mixture of succinic dihydrazide **1** (1.46 g, 10 mmoles) and 3-benzyloxybenzaldehyde (4.2, 20 mmoles) in 50 ml absolute ethanol was refluxed for 3 h. After cooling, the solid crystals were filtered off and recrystallized from dioxane as white crystals.

Synthesis of 1,2-Bis-[5-(3-benzyloxy-phenyl)-1,3,4-oxadiazolyl]-ethane (3). Potassium permanganate (0.5 gm) was added gradually while stirring to compound **2** (0.5 g, 1mmole) in 30 ml acetone. The reaction mixture was refluxed on water bath for 1 h, tells the color of the reaction mixture changed to brown. The reaction mixture was cooled to room temperature and then gradually poured onto crushed ice. On acidification with HCl the solid obtained was filtered off, washed with water, dried and crystallized from acetone as brown crystals.

Synthesis of *N,N′*-Bis-[2-(3-benzyloxy-phenyl)-4-oxo-thiazolidin-3-yl]-succinamide (4). A mixture of compound **2** (2,67 g, 5 mmoles) and 2-mercaptoacetic acid (1 mL, 11 mmoles) in 50 ml benzene in presence of few drops of triethylamine was refluxed for 3 h. After cooling, the reaction mixture was gradually poured onto crushed ice and kept

overnight. The solid formed was filtered off and crystallized from ethanol as yellow crystals.

2,2'-(1,4-Dioxo-1,4-butanediyl)bis(*N*-phenylhydrazine carbothioamide) (5). A mixture of succinic dihydrazide **1** (1.46 g, 10 mmoles) and phenylisothiocyanate (2.7 mL, 20 mmoles) in 100 ml absolute ethanol was refluxed for 3 h. The solid formed on hot was filtered off after cooling, and crystallized from dioxane as pale yellow crystals.

Synthesis of *N,N′*-Bis-(4-oxo-2-phenylimino-thiazolidin-3-yl)-succinamide (6). A mixture of 2,2'-(1,4-Dioxo-1,4-butanediyl)bis(*N*-phenylhydrazine carbothioamide) **5** (2 g, 5 mmoles) and ethyl chloroacetate (1,25 mL, 10 mmoles) in 50 ml absolute ethanol in presence of triethylamine (0.5 ml) was refluxed for 5 h. After cooling, the solid crystals were filtered off and recrystallized from ethanol as white crystals.

Synthesis of *N,N′*-Bis-(4-oxo-2-thioxo-thiazolidin-3-yl)-succinamide (7). A mixture of succinic dihydrazide **1** (1.46 g, 10 mmoles) and thiocarbonyl-bis-thioglycolic acid (4.44 g, 20 mmoles) was fused in an oil bath at 120° for 1/2 h. The residue was washed with ether several times and crystallized from ethanol as yellow crystals.

Synthesis of Phenyl-acetic acid *N′*-[4-oxo-4-(*N′*-phenylacetyl-hydrazino)-butyryl]-hydrazide (8). A mixture of succinic dihydrazide **1** (1. 46 g, 10 mmoles) and phenyl acetic acid (2.7 g, 20 mmoles) was fused in an oil bath at 160° for 1 h. The residue was washed with sod. Carbonate then alcohol and crystallized from dioxane as white crystals.

Synthesis of 1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid *N′*-(4-{*N′*-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetyl]-hydrazino}-4-oxo-butyryl)-hydrazide (9). A mixture of succinic dihydrazide **1** (1.46 g, 10 mmoles) and ethyl *N*-phthaloylglycine (4.66 g, 20 mmoles) was fused in an oil bath at 150° for 1/2 h. The residue was washed with alcohol and crystallized from Acetic acid as pale brown crystals.

Synthesis of 1,4-Bis-(5-amino-3-oxo-2,3-dihydro-pyrazol-1-yl)-butane-1,4-dione (10). A mixture of succinic dihydrazide **1** (1.46 g, 10 mmoles) and ethyl cyanoacetate (2.2 mL, 20 mmoles) in 50 ml dioxane in presence of few drops of piperidine was refluxed for 5 h. After cooling, the reaction mixture was gradually poured onto crushed ice and kept overnight. The solid formed was filtered off and crystallized from ethanol as pale brown crystals.

Synthesis of *N,N'*-Bis-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-succinamide (11) and *N,N′*-Bis-(1,3-dioxo-1H,3H-benzo[de]isoquinolin-2-yl)-succinamide (12): General procedure; A mixture of succinic dihydrazide 1 (1.46 g, 10 mmoles) and phthalic anhydride or 1,8-naphthalic anhydride (20 mmoles) in 50 ml glacial acetic acid was refluxed for 5 h. After cooling, the solid formed was filtered off, washed with water, dried and crystallized from acetic acid/ water (1:4) to give compound **11** as white crystals or **12** as pale brown crystals respectively.

Synthesis of 1,4-Bis-(3-hydrazono-1,3-dihydro-indolyl-2-one)-butane-1,4-one (13). A mixture of succinic dihydrazide **1** (1.46 g, 10 mmoles) and isatin (2.94 g, 20 mmoles) in 50 ml glacial acetic acid was refluxed for 1 h. After cooling, the solid formed was filtered off, washed with water, dried and crystallized from ethanol as yellow crystals.

4 Conclusion

In this report, succinic acid dihydrazide **1** has been utilized as a building block in the synthesis of some novel heterocyclic compounds. Such compounds showed an antibacterial activity, thus the antimicrobial activity screening revealed that compounds **2- 13** have significantly antimicrobial activity, however the compound **12** is the most active against gram (-ve) bacteria. Also, compounds **2**, **3**, **6** and **9** showed good inhibition effect, while these compounds showed moderate inhibition effect against gram (+ve) bacteria, and the data indicate the compounds **2- 13** are biologically inactive against fungi. Finally, we can recommend that, the compounds **2**, **3**, **6**, **9** and **12** are potential sources of bioactive compounds and should be investigated for natural antimicrobial.

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