Egypt. J. Chem. **Vol. 59**, No.5, pp. 867– 885 (2016)

Synthesis, Thermolysis, Photolysis and Antimicrobial Evaluation of some Novel Semicarbazones and Thiosemicarbazones Derived from 3-Methyl-2- benzothiazolinone Hydrazone.

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REACTION of 3-methyl-2-benzothiazolinone hydrazone (1) with some selected isocyanate and isothiocyanate reagents 2a−j gave the respective semicarbazones and thiosemicarbazones 3a−j. Thermolysis of compound 3a under reduced pressure gave N,N`−diethylurea (4) in addition to 1,2-bis(3-methylbenzo[d]thiazol-2(3H)-ylidene)hydrazine (5). Compound 3a was almost quantitatively recovered upon its exposure to sunlight in methanol for 60 days. Elementary and spectroscopic measurements (IR, ^{1}H NMR, ^{13}C NMR, MS) are in good accord with the structures postulated for the new compounds. The single crystal X-ray crystallographic analysis of 3f was given and its data were discussed. The synthesized compounds 3a-j as well as the hydrazone 1 were screened for their antibacterial properties against *Bacillus subtilis* (G^{+}), *Escherichia coli* (G^{-}), *Pseudomonas aeruginosa* (G^{-}) and *Staphylococcus aureus* (G^{+}) and for their antifungal properties against *Aspergillus flavus* and *Candida albicans*. Some of the tested compounds showed an activity against the four bacterial strains where their order of activity was found to be 1 > 3g > 3j > 3i > 3e > 3h > 3a. The MIC_{90} value of compound 1 against *P. aeruginosa* was 9 mg/ml. On the other hand only compound 1 showed a significant activity against *A. flavus* fungal species where it recorded an inhibition zone diameter value (16 mm/mg) which is very near to that of the standard drug, amphotericin B (17 mm/mg). However, the *C. albicans* was found to be insensitive to all of the investigated compounds.

Keywords: 3-Methyl-2-benzothiazolinone hydrazone, Semicarbazones, Thiosemicarbazones, Azines, X-ray crystallographic analysis, Antimicrobial activity.

Antimicrobials are one of a very important category of drugs which are prescribed right from simple infections to the serious diseases. But the microbial resistance towards the drug creates a very serious problem where many drugs which were very effective before are now useless. Moreover, the toxic effects produced by these antibiotics are also reducing their significance.[1,2] So the need for new antimicrobials is always there. Some of most interesting classes of

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compounds, in organic chemistry, are the semicarbazones and thiosemicarbazones due to their significant antibacterial and antifungal activities [3–6]. For example, nitrofural (other names include: nitrofurazone and furacilin; trade name: Furacin) (Fig. 1) is a semicarbazone derivative which is known to have a bactericidal activity. Nitrofural is used topically for skin infections where it was found to be effective on the most of infectious microorganisms [7].

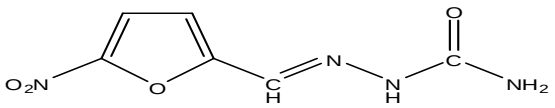


Fig. 1. Nitrofural (Furacin).

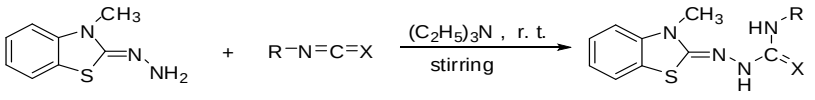
Moreover, recent works have revealed that semicarbazones exhibited many other pharmacological activities including anticonvulsant [8–10], anti-tubercular[11], antitumor,[12] anticancer[13], analgesic and anti−inflammatory activities[14]. On the other hand, benzothiazole derivatives showed diverse pharmacological potentialities such as antimicrobial [15–17], antiviral [18], anticancer[19], antitumor[20], anthelmintic[21], anti-inflammatory[22] and anti-diabetic[22,23] activities. Therefore, such wide range of activities, including semicarbazones and benzothiazoles, has motivated us to synthesize new compounds incorporating both moieties in one structure and evaluating their antimicrobial activity.

Results and Discussion

Chemistry

Synthesis of the semicarbazones and thiosemicarbazones 3a-j

The semicarbazones 3a-e were synthesized by reacting 3-methyl-2-benzothiazolinone hydrazone (1) with the appropriate isocyanate reagent 2a-e in dry 1,4-dioxane at room temperature (Scheme 1).



1 **2a-j** **3a-j**

2 and **3**	**R**	**X**
a	C_2H_5	O
b	$C(CH_3)_3$	O
c	4-Cl-C_6H_4	O
d	3,4-$(Cl)_2$-C_6H_3	O
e	4-NO_2-C_6H_4	O
f	C_2H_5	S
g	C_6H_5	S
h	C_6H_5-(CO)	S
i	4-(CH_3O)-C_6H_4	S
j	2-CH_3-C_6H_4	S

Scheme 1. Synthesis of the semicarbazones and thiosemicarbazones 3a−j.

Compound 3a, namely, N-ethyl-2-(3-methylbenzo[d]thiazol-2(3H) ylidene) hydrazine- carboxamide, taken as an example, was given the assigned structure due to the following reasons

a) Compatible elementary microanalysis corresponded to a molecular formula of $C_{11}H_{14}N_4OS$ (250.32).

b) The IR spectrum (KBr, ν_{max}, cm^{-1}) of **3a** showed strong absorption bands at 3369 (N—H), 3130 (C—H, aromatic), 2962 (C—H, aliphatic), 1653 (C=O), 1610 (C=N, exocyclic) and 1585 (C=C, aromatic).

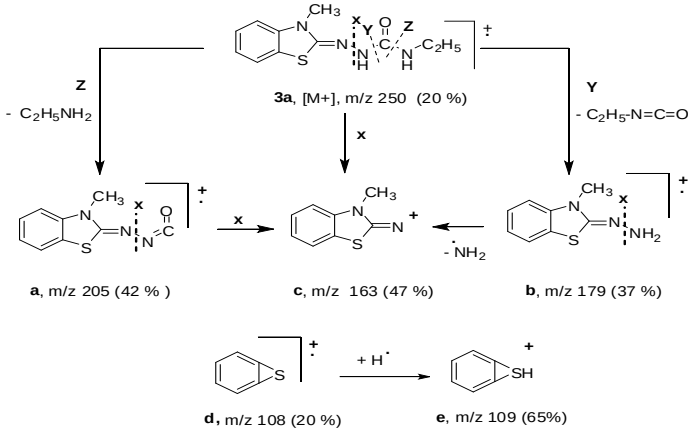
c) The ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ ppm) of **3a** showed a triplet (3H) at 1.02 ppm and a quartet (2H) at 3.11 ppm, both with J_{HH}=6.9 Hz, due to the protons of –C***H***$_3$ and –C***H***$_2$- groups, respectively, of the ethyl group. The methyl group on the nitrogen atom of the fused thiazole ring appeared as a singlet at δ 3.46 ppm. The four aromatic protons of the benzothiazole ring appeared as two doublets (J_{HH} = 7.6 Hz) at 7.15 and 7.53 ppm and as two triplets (J_{HH} = 7.6 Hz) at 7.01 and 7.28 ppm. The spectrum revealed also the presence of two singlet signals at δ 6.40 and 8.21 ppm due to the two D_2O exchangeable protons on nitrogen atoms.

d) The ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ ppm) of semicarbazone **3a**, exhibited three signals in the region of sp^3 carbons at 16.29 , 31.00 and 34.50 ppm due to the carbon atoms of groups (-***C***H$_3$), (N-***C***H$_3$) and (-***C***H$_2$-), respectively. The two signals that appeared at δ 158.71 and 160.96 ppm are attributed to ***C***=O and ***C***=N groups, respectively. Carbon atoms of the fused benzene ring appeared as six signals at 109.78, 121.52, 122.50, 122.83, 127.06 and 141.77 ppm.

e) The mass spectrum (MS: m/z, (%)) of **3a** recorded the molecular ion peak [M^+] at *m/z* 250 (20 %) (Scheme 2). Loss of a neutral ethyl amine molecule from [M^+] yields the radical cation **a** at m/z 205 (42 %). Meanwhile, loss of an ethyl isocyanate molecule from [M^+] produces the radical cation **b** of the starting hydrazone at m/z 179 (37 %). Cleavage of [M^+], ion **a** and / or ion **b** at axis **x** can afford cation **c** at m/z 163 (47 %). The prominent ion peak present at m/z 108 (20 %) coincides with the episulphide species **d** which could result from cleavage of the thiazole ring under electron bombardment. The latter ion can add a hydrogen radical to give cation **e** at m/z 109 (65 %) (Scheme 2).

Similarly, the reaction of the isothiocyanate reagents 2f-j with hydrazone 1 in 1,4-dioxane gave the corresponding thiosemicarbazone derivatives 3f-j (Scheme 1). The IR spectrum (KBr, ν_{max}) of N-ethyl-2-(3-methylbenzo[d]thiazol-2(3H)-ylidene)hydrazinecarbothioamide (3f), as an example, showed a strong absorption band at 1160 cm^{-1} due to the C=S group. The spectrum recorded also bands at 3288 (N—H), 3093 (C—H, aromatic), 2927 (C—H, aliphatic), 1599 (C=N), 1535 (C=C, aromatic) cm^{-1}. The ^{1}H NMR spectrum (500 MHz, DMSO-d_6) recorded three signals at δ 1.10 (t, J_{HH} = 9.0 Hz, 3H), 3.45 (s, 3H) and 3.52 (q, J_{HH} = 9.0 Hz, 2H) ppm due to proton of the -C*H*$_3$, N-C*H*$_3$ and -C*H*$_2$- groups,

respectively. The signals due to the four aromatic protons appeared at δ 7.09 (t, J_{HH} = 6.9 Hz), 7.20 (d, J_{HH} = 6.9 Hz), 7.35 (t, J_{HH} = 6.9 Hz) and 7.58 (d, J_{HH} = 6.9 Hz) ppm. The two protons on nitrogen atoms appeared as two singlets at δ 7.75 (1H) and 9.80 (1H) ppm which disappeared upon running the ^{1}H NMR experiment in presence of D_2O. The ^{13}C NMR spectrum (125 MHz, DMSO-d_6) of 3f disclosed a signal at δ 178.41 ppm due to the carbon atom of *C*=S bond.[24] The signals due to the two carbon atoms of the ethyl group appeared at δ 15.33 (-*C*H_3) and 38.78 (-*C*H_2-) ppm. The spectrum revealed also signals at δ 31.21 (N-*C*H_3), 110.21, 121.97, 122.37, 122.91, 127.22, 141.41 (aromatic carbons), 162.18 (*C*=N) ppm. The molecular weight determination (MS: 70 eV, EI) of 3f has recorded the molecular ion peak at m/z 266 (83 %) which corresponded to a molecular formula of $C_{11}H_{14}N_4S_2$. Moreover, the structure of compound 3f is confirmed by the single crystal X-ray crystallography. Figure 2 showed an ORTEP overview of 3f. The crystal structural data, selected bond lengths, bond angels and torsion angels of 3f are represented in Tables 1, 2, 3 and 4, respectively.



Scheme 2. Mass spectrum of compound 3a.

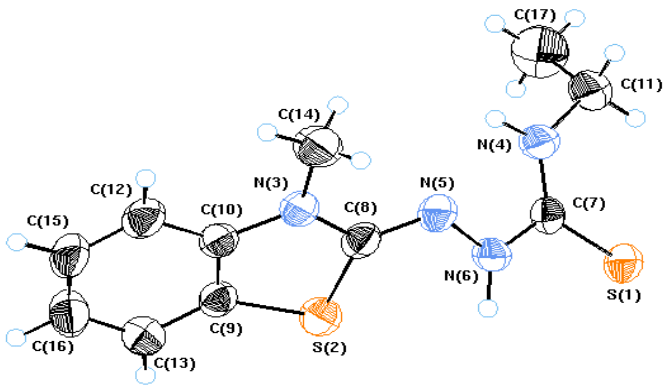


Fig. 2. ORTEP overview of compound 3f.

TABLE 1. Crystal structure and data refinement of compound 3f.

Empirical Formula	$C_{11}H_{14}N_4S_2$
Formula Weight	266.389
Crystal System / Space Group	Monoclinic / $P2_1/c$
a / Å	12.7989 (5)
b / Å	8.4166 (4)
c / Å	14.0071 (12)
α / º	90.00
β / º	12. (18) x 10^1
γ / º	90.00
V / $Å^3$	1296.87 (13)
Z	4
D_{calc} (g/cm^3)	1.364
μ (mm^{-1})	0.39
Colour / Shape	Colourless / needles
Wavelength	Mo *Ka* (0.71073 Å).
Temperature	298 K
Theta range for collection / º	2.910—27.485
Reflections collected	5158
Independent reflections	3435
Data / restraints / parameters	1235 / 0 / 154
Goodness of fit on F^2	1.629
Final R indices [I > 2σ (I)]	0.042
R indices (all data)	0.152
Largest difference peak / hole	0.73 / - 0.66

TABLE 2. Selected bond lengths (Å) of compound 3f.

S1 – C7	1.709 (2)	N5 – C8	1.299 (2)
S2 – C8	1.750 (2)	N6 – C7	1.355 (2)
S2 – C9	1.756 (2)	C9 – C10	1.388 (3)
N3 – C8	1.371 (2)	C9 – C13	1.378 (3)
N3 – C10	1.401 (3)	C10 – C12	1.392 (3)
N3 – C14	1.447 (3)	C11 – C17	1.489 (3)
N4 – C7	1.317 (3)	C12 – C15	1.381 (4)
N4 – C11	1.453 (3)	C13 – C16	1.381 (3)
N5 − N6	1.416 (2)	C15 – C16	1.370 (4)

TABLE 3. Selected bond angels (degree) of compound 3f.

C8 − S2 − C9	90.81 (11)	C12—C15—C16	121.90 (2)
C8− N3 − C10	114.00 (2)	S2 – C8 – N5	128.10 (2)
C8 − N3 – C14	121.90 (2)	N3 − C8 − N5	120.70 (2)
C10 – N3 – C14	124.00 (2)	S2 − C9 − C10	111.10 (2)
C7 – N4 – C11	125.40 (2)	S2 − C9 − C13	127.90 (2)
N6 – N5 – C8	112.00 (2)	C10 − C9 − C13	121.00 (2)
N5 – N6 – C7	117.30 (2)	N3—C10—C9	112.70 (2)
S1 – C7 – N4	124.00 (2)	N3—C10—C12	127.00 (2)
S1 – C7 – N6	118.70 (2)	C9—C10—C12	120.30 (2)
N4 – C7 – N6	117.20 (2)	N4—C11—C17	112.40 (2)
S2 – C8 – N3	111.20 (2)	C10—C12—C15	117.70 (2)
C9—C13—C16	118.60 (2)	C13—C16—C15	120.40 (2)

TABLE 4. Selected torsion angels (degree) of compound 3f.

C9—S2—C8—N3	4.4 (3)	C12—C10—N3—C14	-0.1 (4)
C9—S2—C8—N5	-175.0 (4)	N3—C10—C12—C15	178.4 (6)
C8—S2—C9—C10	-3.2 (3)	C12—C10—C9—S2	-179.1 (5)
C10—N3—C8—S2	-4.6 (3)	C12—C10—C9—C13	1.0 (4)
C10—N3—C8—N5	174.8 (5)	C9—C10—C12—C15	-1.2 (4)
C8—N3—C10—C9	2.2 (3)	C17—C11—N4—C7	114.1 (5)
C8—N3—C10—C12	-177.5 (6)	C10—C12—C15—C16	0.7 (4)
C14—N3—C8—S2	177.9 (5)	C16—C13—C9—S2	180.0 (6)
C14—N3—C8—N5	-2.6 (4)	C16—C13—C9—C10	-0.1 (4)
C14—N3—C10—C9	179.6 (5)	C9—C13—C16—C15	-0.5 (4)
C14—N3—C10—C12	-0.1 (4)	C16—C15—C12—C10	0.7 (4)
C11—N4—C7—S1	1.7 (3)	C12—C15—C16—C13	0.2 (4)
C11—N4—C7—N6	-177.0 (5)	C15—C16—C13—C9	-0.5 (4)
C7—N4—C11—C17	114.1 (5)	C13—C16—C15—C12	0.2 (4)
N6—N5—C8—S2	-2.2 (3)	C7—N6—C8—N5	-59.4 (4)
N6—N5—C8—N3	178.5 (5)	N4—C7—N6—N5	-9.7 (3)
C8—N5—N6—C7	140.5 (4)	S2—C8—N5—N6	-2.2 (3)
N5—N6—C7—S1	171.6 (4)	S2—C9—C10—N3	1.3 (3)
N5—N6—C7—N4	-9.7 (3)	C12—C10—N3—C8	-177.5 (6)
C7—N6—N5—C8	140.5 (4)	C9—C10—N3—C14	179.6 (5)
C9—C10—N3—C8	2.2 (3)	N3—C10—C9—C13	-178.7 (5)

The C7—S1 bond distance of 1.709 (2) Å is being intermediate between 1.82 Å for C—S single bond and 1.56 Å for C=S double bond[25] (Fig. 2 and Table 2). Moreover, the two C7—N4 and C7—N6 bonds have distance values of 1.317 (3) and 1.355 (2) Å, respectively, which are intermediate between 1.47 Å for C—N single bond and 1.28 Å for C=N double bond [26]. These bond distances are indicative of some double bond character of C7—S1, C7—N4 and C7—N6 bonds, suggesting an extensive electron delocalization involving the N6—C7(S1)—N4 moiety (Fig. 3). Apparently, such delocalization may be enhanced by the almost planarity of these bonds where the torsion angels C11—N4—C7—S1, N5—N6—C7—S1 and N5—N6—C7—N4 have values of 1.7 (3), 171.6 (4) and -9.7 (3)º which are very close to 0 and/or 180º. However, the N5—N6 and N5—C8 bonds have almost retained their single and double bonding characters where they have bond distance values of 1.416 (2) and 1.299 (2) Å (Table 2), respectively[26]. Moreover, the C=S and N−N bonds exhibited the *E*−configuration where they are *trans* to each other (Fig. 2 & 3).

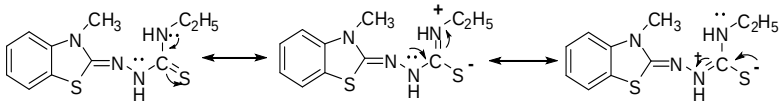
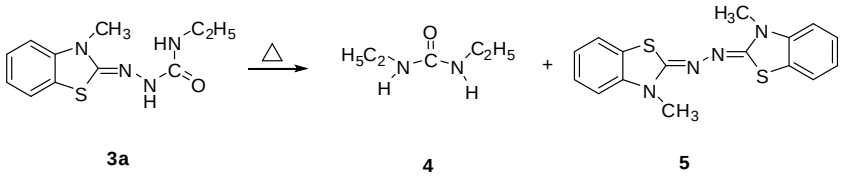


Fig. 3. The electronic resonance of compound 3f.

Effect of heat and sunlight on the semicarbazone 3a

When compound 3a was heated in a cold finger sublimator at 220 °C (bath temperature) under reduced pressure for 30 min, two different substances were produced (Scheme 3). The colourless needles that sublimed were identified as N, N`-diethylurea (4)[27,28] by m.p., mixed m.p., comparative IR and MS spectra. Purification of the remained substance gave a yellow crystalline compound which was proved to be 1,3-bis(3-methylbenzo[d]thiazol-2(3H)-ylidene) hydrazine (5)[29] (Scheme 3). An ORTEP overview of compound 5 is represented in Fig. 4 [29] .



3a **4** **5**

Scheme 3. Thermolysis of compound 3a.

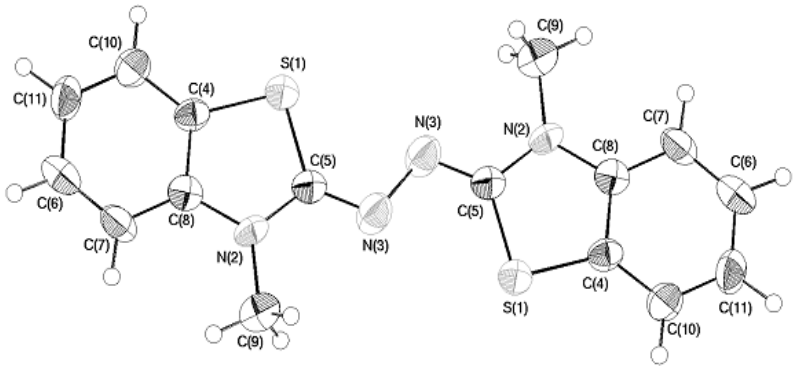


Fig. 4. An ORTEP overview of the azine 5.

Previous works[30–32] reported that, thermolysis of semicarbazones (A) occurs through formation of the reactive N-substituted isocyanate intermediates (B) followed by the unstable N-substituted isocyanate dimmers (C) which can be converted *in situ* to the corresponding azines (D) (Fig. 5)[30,31] in addition to the N-substituted ureas, carbamates and/or β-lactams.

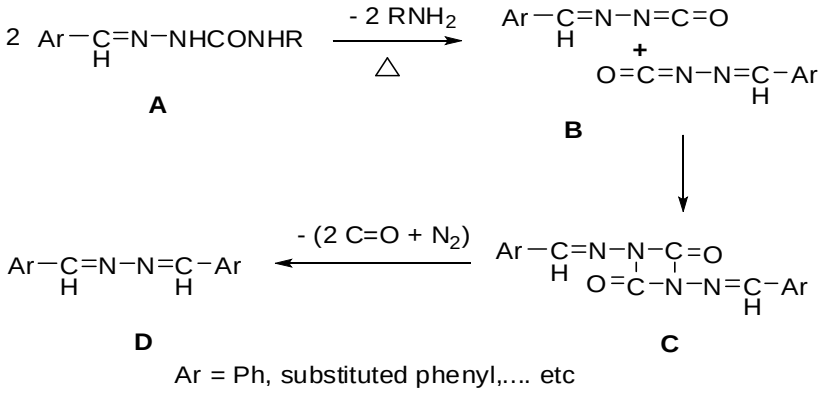


Fig. 5. Thermolysis of semicarbazones.

On the other hand, the semicarbazone 3a was found to be highly stable against light. Thus, compound 3a was almost quantitatively recovered (92 %) (m.p., mixed m.p., comparative MS and IR spectra) after its exposure to sun light in methanol for 60 days (September – October).

The Antimicrobial evaluation of compounds 1 and 3a-j

The newly synthesized semicarbazones and thiosemicarbazones 3a-j as well as the starting hydrazone 1 were screened *in vitro* against two Gram +ve bacteria (as *Bacillus subtilis* and *Staphylococcus aureus*), two Gram –ve bacteria (as *Escherichia coli* and *Pseudomonas aeuroginosa*) and two fungal species (as *Aspergillus flavus* and *Candida albicans*) by using a modified Kirby−Bauer disc diffusion method [33]. Ampicillin and Amphotericin B were taken as reference drugs for antimicrobial and antifungal screenings, respectively. The results expressed as the inhibition zone diameter (mm / mg Sample) are compiled in Table 5 and represented in Fig. 6. Among the tested compounds, hydrazone (1) was found to be the most active against the four screened bacterial species. Meanwhile, among the ten synthesized compounds 3a-j, the thiosemicarbazone (3g) exhibited the highest activity followed by compounds 3j and 3i which showed a moderate activity. The MIC_{90} value for compound 1 was determined using agar dilution method where it recorded a value of 9 mg/ml against *Pseudomonas aeuroginosa*. Moreover, the tested bacterial species were found to be slightly sensitive for compounds 3a, 3e and 3h except for *Staphylococcus aureus* which is insensitive for the semicarbazone 3a. Compounds 3b, 3c, 3d and 3f were found to be inactive against the four screened bacterial strains. On the other hand, the tested compounds were found to be inactive against the two screened fungal species except for compound 1. It showed a high activity only against *Aspergillus flavus* where it recorded an inhibition zone diameter value of 16 (mm/mg) which is very close to that of the standard drug, amphotericin B (17 mm/mg) (Table 5 and Fig. 6). The moderate and /or negative antimicrobial activity of the synthesized hydrazones 3a−j might come from their high electron density caused by the mesomeric effect (Fig. 3) which make the diffusion of

these compounds more difficult through the body of the bacteria [34,35].

Conclusion

In the present investigation, we have successfully synthesized a series of novel semicarbazone and thiosemicarbazone derivatives through a simple and direct method by reacting 3-methyl-2-benzothiazolinone hydrazone (1) with some seleceted isocyanate and isothiocyanate reagents. The new synthesizes products (3a−j) are fully characterized through the spectral (^{1}H NMR, ^{13}C NMR, IR, MS) and X−ray crystallographic studies. The −N−N− bond in 3a is the most vulnerable site of attack due to thermolysis leading to N,N−diethylurea (4) in addition to the dimeric product 5. On the other hand, compound 3a exerted a high stability against the solar UV−irradiation where it was quantitatively recovered after a long exposure period (60 days). Some of the synthesized compounds as well as the starting hydrazone **1** were found to exert antimicrobial activity against *B. subtilis* (G^{+}), *E. coli* (G^{-}), *P. aeruginosa* (G^{-}) and *S. aureus* (G^{+}), *A. flavus* and/or *C. albicans* microbial strains.

TABLE 5. The antimicrobial activity of the hydrazone 1 and the synthesized semicarbazone and thiosemicarbazone derivatives 3a-j expressed in inhibition zone diameter (mm / mg Sample).

Sample	Inhibition zone diameter (mm / mg Sample)					
	Bacillus subtilis **(G^{+})**	***Escherichia coli*** **(G^{-})**	***Pseudomonas aeruginosa*** **(G^{-})**	***Staphylococcus aureus*** **(G^{+})**	***Aspergillus flavus*** **(Fungus)**	***Candida albicans*** **(Fungus)**
Ampicillin*	21	21	22	19	--	--
Amphotericin B**	-- --	--	--	--	17	20
1	17	17	18	16	16	0.0
3a	9	9	9	0.0	0.0	0.0
3b	0.0	0.0	0.0	0.0	0.0	0.0
3c	0.0	0.0	0.0	0.0	0.0	0.0
3d	0.0	0.0	0.0	0.0	0.0	0.0
3e	10	9	9	10	0.0	0.0
3f	0.0	0.0	0.0	0.0	0.0	0.0
3g	15	14	14	13	0.0	0.0
3h	9	9	9	9	0.0	0.0
3i	12	11	11	11	0.0	0.0
3j	13	13	14	12	0.0	0.0

Standards: * antibacterial agent − ** antifungal agent

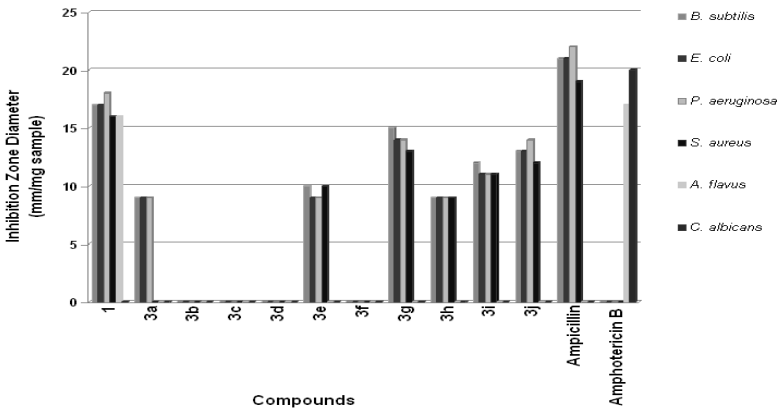


Fig. 6. The antimicrobial evaluation for compound 1 and derivatives 3a-j.

Experimental

General

The reactions of airsensitive reagents were carried out in flame-dried glassware under an atmosphere of dry argon. Solvents were purified and dried according to usual procedures. 3-Methyl-2-benzothiazolinone hydrazone (**1**) was prepared according to a known procedure[36] . Isocyanates and isothiocyanates are commercially available. The photo experiment was carried out in Schlenk tube of Pyrex glass. The tubes were sealed while a stream of dry nitrogen was passing through. Melting points were recorded on an electrothermal melting point apparatus and were uncorrected. The infrared spectra were obtained from KBr-disks using JASCO FT/IR-300E Fourier Transformation Infrared Spectrophotometer and reported in cm^{-1}. The ^{1}H NMR spectra were recorded on JEOL 500 ECA (running at 500 MHz) and/or JEOL JNM-EX 270 (running at 270 MHz). The ^{13}C NMR spectra were recorded on JEOL 500 ECA (running at 125 MHz). Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane (TMS). Mass spectra were recorded on Finnigan SSQ 7000 Spectrometer at 70 eV. The elemental analyses were carried out at the Micro Analytical Unit, Cairo University, Egypt. X-ray diffraction: Intensity data collection were performed with Kappa-CCD Enraf Nonius FR 590 Single crystal Diffractometer. The structures were solved by direct methods using the *SIR92* program[37] and refined using ma*X*us [38]. The molecular graphics were made with ORTEP[39]. Crystallographic data (CIF) for the structure reported in this article has been deposited in the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication No.1494262. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (FAX: +44 (1223) 336-033; E-mail: deposite@ccdc.cam.ac.uk). The antimicrobial evaluation was carried out at the Micro Analytical Centre, Faculty of Science, Cairo University, Cairo, Egypt.

Chemistry

Synthesis of 2-(3-methylbenzo[d]thiazol-2(3H)-ylidene)hydrazinecarboxamide derivatives 3a-j.

To a stirred solution of hydrazone (1) (0.005 mole, 0.9 g) in dry 1,4-dioxane, the appropriate isocyanate and/or isothiocyanate reagent (2a-j) (0.01 mole) was added followed by few drops of triethylamine under dry argon atmosphere. The reaction mixture was stirred for 24 hr at room temperature where the materials that precipitated were collected, washed with cold diethyl ether and recrystallized from the appropriate solvent to give compounds 3a-j, respectively.

N-Ethyl-2-(3-methylbenzo[d]thiazol-2(3H)-ylidene)hydrazinecarboxamide (3a)

Colorless crystals yield: 88 % (1.1 g), m.p. 200 ºC (acetonitrile). IR (KBr, ν_{max}, cm^{-1}): 3369 (N—H), 3130 (C—H, aromatic), 2962 (C—H, aliphatic), 1653 (C=O), 1610 (C=N, exocyclic), 1585 (C=C, aromatic). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.02 (t, J_{HH} = 6.9 Hz, 3H, CH_2-C***H***$_3$), 3.11 (q, J_{HH} = 6.9 Hz, 2H, C***H***$_2$-CH_3), 3.46 (s, 3H, N-C***H***$_3$), 6.40 (s, 1H, N***H***, D_2O exchangeable), 7.01 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.15 (d, J_{HH} = 7.6 Hz, 1H benzothiazole ring), 7.28 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.53 (d, J_{HH} = 7.6 Hz, 1H benzothiazole ring), 8.21 (s, N***H***, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 16.29 (CH_2-***C***H_3), 31.00 (N-***C***H_3), 34.5 (***C***H_2-CH_3), 109.78, 121.52, 122.50, 122.83, 127.06, 141.77 (aromatic carbons), 158.71 (***C***=O), 160.96 (***C***=N). MS (EI, 70eV): m/z (%) = 250 (20) [M^+]. Anal. Calcd (%) for $C_{11}H_{14}N_4OS$ (250.32): C, 52.78; H, 5.64; N, 22.38; S, 12.81. Found (%): C, 52.85; H, 5.60; N, 22.32 S, 12.78.

N-tert-Butyl-2-(3-methylbenzo[d]thiazol-2(3H)-ylidene)hydrazinecarboxamide (3b)

Colorless crystals, yield: 86 % (1.2 g), mp 206 ºC (acetonitrile). IR (KBr, ν_{max}, cm^{-1}) : 3302 (N—H), 3095 (C—H, aromatic), 2964 (C—H, aliphatic), 1658 (C=O), 1613 (C=N, exocyclic), 1570 (C=C, aromatic). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.29 (s, 9H, C-(C*H*$_3$)$_3$), 3.43 (s, 3H, N-C*H*$_3$), 5.79 (s, N*H*, D_2O exchangeable), 7.02 (t, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 7.15 (d, J_{HH} = 8.1 Hz, 1H, benzothiazole ring), 7.29 (t, J_{HH} = 8.1 Hz, 1H, benzothiazole ring), 7.54 (d, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 8.09 (s, 1H, N*H*, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 29.59 (C(***C***H_3)$_3$), 30.97 (N-***C***H3), 49.89 (***C***(CH_3)$_3$), 109.83, 121.54, 122.43, 122.83, 127.09, 141.65 (aromatic carbons), 157.67 (***C***=O), 159.92 (***C***=N). MS (70eV): m/z (%) = 278 (32) [M^+]. Anal. Calcd (%) for $C_{13}H_{18}N_4OS$ (278.37): C, 56.09; H, 6.52; N, 20.13; S, 11.52. Found (%): C, 56.17; H, 6.50; N, 20.08; S, 11.56.

N-(3-Chlorophenyl)-2- (3-methylbenzo[d]thiazol-2 (3H)-ylidene) hydrazine-carboxamide (3c)

Colourless crystals, yield: 72 % (1.2 g), m.p. 186 °C (acetonitrile). IR (KBr, ν_{max}, cm^{-1}): 3303 (N—H), 3160 (C—H, aromatic), 1708 (C=O), 1670 (C=N), 1583 (C=C, aromatic), 765 (C—Cl, aromatic). ^{1}H NMR (270 MHz, DMSO-d_6, δ

ppm): 3.45 (s, 3H, N-C*H*$_3$), 5.45 (s, N*H*, D_2O exchangeable), 6.50 (d, J_{HH} = 7.6 Hz, 1H, aromatic), 7.02 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.07 (t, J_{HH} = 7.6 Hz, 1H, aromatic), 7.17 (d, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.29 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7. 45 (d, J_{HH}=7.6 Hz, 1H, aromatic), 7.54 (d, J_{HH} = 7.6 Hz , 1H, benzothiazole ring), 7.71 (s, 1H, aromatic), 7.80 (s, 1H, N*H*, D_2O exchangeable). MS (70eV): m/z (%) = 332 (8) (based on ^{35}Cl) and 334 (3) (based on ^{37}Cl) [M^+]. Anal. Calcd (%) for $C_{15}H_{13}ClN_4OS$ (332.81): C, 54.13; H, 3.94; Cl, 10.65; N, 16.83; S, 9.63. Found (%): C, 54.04; H, 3.97; Cl, 10.57; N, 16.78; S, 9.67.

N-(3,4- Dichlorophenyl)-2- (3-methylbenzo [d]thiazol-2 (3H) -ylidene) hydrazinecarbox- amide (3d)

Colourless crystals, yield 76 % (1.4 g), m.p. 226-228 °C (1,4-dioxane). IR (KBr, ν_{max}, cm^{-1}): 3355, 3190 (N—H), 3065 (C—H, aromatic), 2920 (C—H, aliphatic), 1677 (C=O), 1626 (C=N), 1576 (C=C, aromatic), 740 (C—Cl, aromatic). ^{1}H NMR (270 MHz, DMSO-d_6, δ ppm): 3.45 (s, 3H, N-C***H***$_3$), 7.05 (t, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 7.22 (d, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 7.32 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.50 (d, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.58-7.63 (m, 2H, aromatic), 7.98 (s, 1H, aromatic), 8.70 (s, 1H, N***H***, D_2O exchangeable), 9.05 (s, 1H, N***H***, D_2O exchangeable). MS (70eV, EI): m/z (%) = 366 (30) [M+] (based on 2^{35}Cl), 368 (20) [M^++2] (based on ^{35}Cl + ^{37}Cl), 370 (3) [M^+ + 4] (based on 2 ^{37}Cl). Anal. Calcd (%) for: $C_{15}H_{12}Cl_2N_4OS$ (367.25): C, 49.06; H, 3.29; Cl, 19.31; N, 15.26; S, 8.73. Found (%): C, 49.06; H, 3.29; Cl, 19.31; N, 15.26; S, 8.73.

2-(3-Methylbenzo[d]thiazol-2 (3H)-ylidene)-N- (4-nitrophenyl) hydrazine-carboxamide (3e)

Yellow crystals, yield: 52 % (0.9 g), m.p. 272 – 274 °C (1,4-dioxane). IR (KBr, ν_{max}, cm^{-1}): 3367, 3337 (N—H), 3067 (C—H, aromatic), 1698 (C=O), 1632 (C=N), 1598 (C=C, aromatic), 1533, 1330 (NO_2). ^{1}H NMR (270 MHz, DMSO-d_6, δ ppm): 3.42 (NC***H***$_3$), 7.09 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.17 – 7.62 (m, 5H, aromatic and benzothiazol ring), 8.07 (d, J_{HH}=7.6 Hz, 2H, aromatic), 9.57 (s, 1H, N***H***, D_2O exchangeable), 10.14 (s, 1H, N***H***, D_2O exchangeable). MS (70eV): m/z (%) = 343 (10). Anal. Calcd (%) for: $C_{15}H_{13}N_5O_3S$ (343.36): C, 52.47; H, 3.82; N, 20.40; S, 9.34. Found (%): C, 52.40; H, 3.85; N, 20.36; S, 9.30.

N-Ethyl-2-(3-methylbenzo[d]thiazol-2(3H)-ylidene)hydrazinecarbothioamide (3f)

Colourless needles yield: 69 % (0.9 g), mp 195 ºC (acetonitrile). IR (KBr, ν_{max}, cm^{-1}): 3288 (N—H), 3093 (C—H, aromatic), 2927 (C—H, aliphatic), 1599 (C=N), 1535 (C=C, aromatic), 1160 (C=S). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 1.10 (t, J_{HH} = 9.0 Hz, 3H, CH_2CH_3), 3.45 (s, 3H, N-C*H*$_3$), 3.52 (q, J_{HH} =9.0 Hz, 2H, CH_2-CH_3), 7.09 (t, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 7.20 (d, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 7.35 (t, J_{HH} = 6.9 Hz, 1H, benzothiazole

ring), 7.58 (d, J_{HH}= 6.9 Hz, 1H, benzothiazole ring), 7.75 (s, 1H, N*H*, D_2O exchangeable), 9.80 (s, 1H, N*H*, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6): 15.33 (CH_2CH_3), 31.21 (N-CH_3), 38.78 (CH_2CH_3), 110.21, 121.97, 122.37, 122.91, 127.22, 141.41 (aromatic carbons), 162.18 (*C*=N), 178.41 (*C*=S). MS (70eV): m/z (%) = 266 (83) [M^+]. Anal. Calcd (%) for $C_{11}H_{14}N_4S_2$ (266.39): C, 49.60; H, 5.30; N, 21.03; S, 24.07. Found (%): C, 49.68; H, 5.27; N, 20.97; S, 24.11.

2-(3-Methylbenzo[d]thiazol-2(3H)-ylidene)-N-phenylhydrazinecarbothioamide (3g)

Pale green crystals, yield: 86 % (1.4 g), mp 176 ºC (acetonitrile). IR (KBr, ν_{max}, cm^{-1}): 3315 (N—H), 3097 (C—H, aromatic), 2920 (C—H, aliphatic), 1620 (C=N, exocyclic), 1580 (C=C, aromatic), 1200 (C=S). ^{1}H NMR (270 MHz, DMSO-d_6, δ ppm): 3.55 (s, 3H, N-CH_3), 7.05 – 7.65 (m, 9H, aromatic and benzothiazole ring), 9.30 (s, 1H, N*H*, D_2O exchangeable), 10.37 (s, 1H, N*H*, D_2O exchangeable). Anal. Calcd (%) for $C_{15}H_{14}N_4S_2$ (314.43): C, 57.30; H, 4.49; N, 17.82; S, 20.40. Found (%): C, 57.37; H, 4.46; N, 17.78; S, 20.44.

N-(Benzoyl)-2- (3-methylbenzo [d]thiazol-2(3H) -ylidene) hydrazine-carbothioamide (3h)

Yellow crystals, yield: 55 % (0.93 g), m. p. 164 (acetonitrile). IR (KBr, ν_{max}, cm^{-1}): 3410, 3247 (N—H), 3060 (C—H, aromatic), 2925 (C—H, aliphatic), 1660 (C=O), 1605 (C=N), 1580 (C=C, aromatic), 1190 (C=S). ^{1}H NMR (270 MHz, DMSO-d_6, δ ppm): 3.57 (NCH_3), 7.10 (t, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 7.30 (d, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 7.38 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.50 (t, J_{HH} = 6.9 Hz, 2H, aromatic), 7.63 – 7.70 (m, 2H, aromatic and benzothiazole ring), 8.00 (d, J_{HH} = 7.6 Hz, 2H, aromatic), 11.50 (s, 1H, N*H*, D_2O exchangeable), 13.00 (s, 1H, N*H*, D_2O exchangeable). MS (70eV, EI): m/z (%) = 342 (10) Anal. Calcd (%) for $C_{16}H_{14}N_4OS_2$ (342.44): C, 56.12; H, 4.12; N, 16.36; S, 18.73. Found (%): C, 56.19; H, 4.10; N, 16.31; S, 18.76.

N-(4-Methoxyphenyl)-2- (3-methylbenzo[d]thiazol -2(3H)-ylidene) hydrazine-carbothio- amide (3i)

Colourless leaflets, yield: 81 % (1.4 g), m.p. 174 (acetonitrile). IR (KBr, ν_{max}, cm^{-1}): 3258 (N—H), 3099 (C—H, aliphatic), 2928 (C—H, aliphatic), 1602 (C=N), 1577 (C=C, aromatic), 1196 (C=S). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 3.54 (s, 1H, N-CH_3), 3.74 (s, 1H, OCH_3), 6.89 (d, J_{HH} = 8.1 Hz, 2H, aromatic, AA`BB` system), 7.09 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.24 (d, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.35 (t, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 7.40 (d, J_{HH} = 8.1 Hz, 2H, aromatic, AA`BB` system), 7.61 (d, J_{HH} = 7.6 Hz, 1H, benzothiazole ring), 9.20 (s, 1H, N*H*, D_2O exchangeable), 10.2 (s, 1H, N*H*, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 31.32 (N-CH_3), 55.76 (OCH_3), 110.36, 113.68, 122.09, 122.38, 122.97, 127.31, 127.46, 132.86, 141.44, 157.12 (aromatic carbons), 162.73 (*C*=N), 177.45 (*C*=S). MS (70eV, EI): m/z (%) = 344 (10). Anal. Calcd (%) for $C_{16}H_{16}N_4OS_2$ (344.45):

C, 55.79; H, 4.68; N, 16.27; S, 18.62. Found (%): C, 55.86; H, 4.64; N, 16.23; O, S, 18.60.

2-(3-Methylbenzo [d]thiazol-2 (3H)-ylidene)-N-o- tolylhydrazine-carbothioamide (3j)

Pale yellow crystals, yield 73 % (1.2 g), m. p. 170 °C (chloroform/petroleum ether b. r. 80-100 °C). IR (KBr, ν_{max}, cm^{-1}): 3270 (N—H), 3074 (C—H, aromatic), 2900 (C—H, aliphatic), 1620 (C=N), 1580 (C=C, aromatic), 1180 (C=S). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 7.07 – 7.35 (m, 7H, aromatic and benzothiazole ring), 7.62 (d, J_{HH} = 6.9 Hz, 1H, benzothiazole ring), 9.12 (s, 1H, N*H*, D_2O exchangeable), 10.24 (s, 1H, N*H*, D_2O exchangeable). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 18.41 (*C*H_3), 31.27 (N-*C*H_3), 110.37, 122.10, 122.39, 123.01, 126.27, 126.76, 127.31, 128.78, 130.49, 135.45, 138.41, 141.47 (aromatic carbons), 163.04 (*C*=N), 177.87 (*C*=S). MS (70eV, EI): m/z (%) = 328 (8). Anal Calcd (%) for $C_{16}H_{16}N_4S_2$ (328.46): C, 58.51; H, 4.91; N, 17.06; S, 19.52. Found (%): C, 58.43; H, 4.96; N, 16.99; S, 19.55.

Thermolysis of compound 3a

The semicarbazone 3a (0.002 mole, 0.5 g) was heated in a cold finger sublimator at 220 ºC (bath temperature) under reduced pressure (0.5 mm/Hg) for 30 min. The substance that sublimed as well as the residue in the sublimator were collected and recrystallized from the appropriate solvent to give compounds **4** and **5**, respectively.

N, N`-Diethylurea (4)

Colourless needles, yield 73 % (0.085 g), m. p. 111 °C (ethanol) [Ref.[27] : 112-113 °C]. IR (KBr, ν_{max}, cm^{-1}): 3310 (N—H), 2920 (C—H, aliphatic), 1635 (C=O). MS (70eV, EI): m/z (%) = 116 (100) [M^+].

1,3-Bis(3-methylbenzo[d]thiazol-2(3H)-ylidene)hydrazine (5)

Yellow crystals, yield 67 % (0.22 g), m.p. 263 °C (toluene) [Ref.[29] : 266 °C]. IR (KBr, ν_{max}, cm^{-1}): 3050 (C—H, aromatic), 2915(C—H, aliphatic), 1610 (C=N), 1570 (C=C, aromatic). MS (70eV, EI): m/z (%) = 326 (100) [M^+].

Photochemical action of sunlight on compound 3a

A solution of 3a (0.01 mole, 2.5 g) in dry methanol (200 mL) was exposed to sunlight for 60 days (September-October). The volatile materials were removed under reduced pressure where the semicarbazone 3a was almost quantitavely recovered (2.3 g, 92 %) after crystallizing the residue from acetonitrile (m.p., mixed m. p., comparative TLC and comparative IR).

The Biological evaluation

The antimicrobial sensitivity test

Antimicrobial activity of the tested samples was determined using a modified Kirby − Bauer disc diffusion method[33]. Briefly, 100 µL of the test bacteria/fungi were grown in 10 ml of fresh media until they reached a count of approximately

108 cells/mL for bacteria or 105 cells/mL for fungi[40]. 100 µL of microbial suspension was spread onto agar (Müller-Hinton agar) plates corresponding to the broth in which they were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from primary agar plates and tested for susceptibility. Plates inoculated with filamentous fungi *as Aspergillus flavus* at 25 ºC for 48 hr; Gram (+) bacteria as *Staphylococcus aureus, Bacillus subtilis*; Gram (-) bacteria as *Escherichia coli, Pseudomonas aeuroginosa* they were incubated at 35-37 ºC for 24-48 hours and yeast as *Candida albicans* incubated at 30 ºC for 24-48 hr. Standard discs of Ampicillin (Antibacterial agent), Amphotericin B (Antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10 µL of solvent (DMSO) were used as a negative control. Blank paper disk with a diameter of 8.0 mm were impregnated with 10µL of the tested chemical and placed on agar where the chemical diffuses from the disc into the agar. When an organism is placed on the agar it will not grow in the area around the disc if it is susceptible to the tested chemical. The area of no growth around the disc is known as the "Zone of inhibition" whose diameter was measured in millimeters with a sterilized slipping calipers.

Determination of minimum inhibitory concentration (MIC_{90}) for compound 1 against P. aeruginosa:

The minimum concentration of a compound which inhibits 90 % of the tested microorganism growth when compared to control (no treatment) is known as MIC_{90}. It is determined by using Agar Dilution Method [41,42]. Briefly, stationary – phase cultures of bacteria were prepared at 37°C and they were used to inoculate a fresh 5.0 ml culture to an OD_{600} value (optical density of the sample measured at wave length of 600 nm) of 0.05. The 5.0 ml cultures were then incubated at 37°C until an OD_{600} of 0.10 was achieved from which standardized bacterial suspensions were prepared to a final cell density of 6×10^5 CFU (the colony forming units) /ml. Serial dilutions from the treatments (0-320 mg/ml) were prepared and mixed with 5.0 ml of the standardized bacteria suspension then added to the plates and incubated for 24 hr at 37°C. The colony forming units (CFU) were counted for each dilution.

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(*Received* 18/7/2016;
Accepted 28/7/2016)

التشييد و التحلل الحرارى و الضوئى و التقييم المضاد للميكروبات لبعض السميكاربازونات و الثيوسميكاربازونات الجديدة المشتقة من 3-مثيل-2-بنزوثيازولينون هيدرازون.

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نظرا للأهمية البيولوجية لمركبات السميكاربازون و الثيوسميكاربازون وخاصة كمضادات للميكروبات و التشنجات العصبية و نمو الأورام السرطانية , فقد عنى هذا البحث بتحضير سلسلة جديدة من مركبات السميكاربازون و الثيوسميكاربازون **3a-j** المشتقة من مركب 3-مثيل-2-بنزوثيازولينون هيدرازون (**1**). وقد تأييدت التركيبات البنائيه للمركبات الجديدة بواسطة التحاليل العنصريه الدقيقه والتحاليل الطيفية المختلفة و منها طيف حيود الأشعة السينية للبلورة المنفردة , كما تمت دراسه تأثير تسخين السميكاربازون **3a** عند درجة حرارةعالية وتحت ضغط منخفض حيث تحلل حراريا مكوناً خليطاً من مركب ن,ن'- ثنائى إيثيل يوريا (**4**) و مزدوج جزيئى 3-(مثيل بنزوثيازوليليدين) هيد رازين (**5**) الذى تم تأييد تركيبه الكيميائى بواسطة طيف حيود الأشعة السينية للبلوره المنفرده فى حين أن نفس المركب **3a** لا يتأثر عند محاولة تحليله ضوئيا حتى بعد تعرضه لضوء الشمس المباشر لمدة ستين يوما. و الى جانب ذلك فقد تم تقييم المادة البادئة و المركبات الجديدة كمضادات للميكروبات حيث وجد لبعض منها نشاطا واعدا كمضادات للبكتيريا . و من ناحيه أخرى فقد أبدت الماده البادئه (هيدرازون **1**) فقط نشاطا قوياً كمضاد للفطريات من نوع *أسبرجيلوس فلافوس* وبفاعلية تقترب من فاعلية العقار القياسى (أمفوتيريسين- ب).