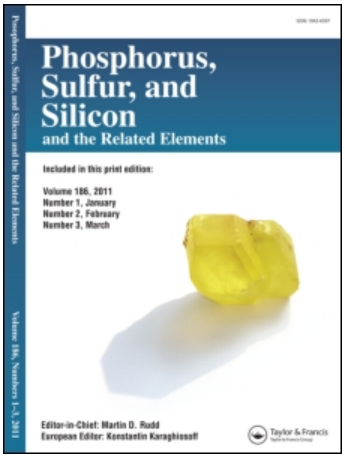

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α,β-Unsaturated γ-Oxo Carboxylic Acids in Heterocylic Synthesis II. Behavior of 4-(5,5-Dioxodibenzothiophen-2-yl)-4-oxo-2-butenoic Acid Towards Carbon Nucleophiles under Michael Reaction Condition

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α,β-UNSATURATED γ-OXO CARBOXYLIC ACIDS IN HETEROCYLIC SYNTHESIS II. BEHAVIOR OF 4-(5,5-DIOXODIBENZOTHIOPHEN-2-YL)-4-OXO-2-BUTENOIC ACID TOWARDS CARBON NUCLEOPHILES UNDER MICHAEL REACTION CONDITION

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*4-(5,5-Dioxodibenzothiophen-2-yl)-4-oxo-2-butenoic acid (**1**) was condensed with compounds containing active methylene groups under Michael reaction conditions to form the Michael adducts **2a–c**, **3a–c**, and **4a–b**. The behavior of Michael adduct towards the action of hydrazine hydrate was investigated. The compounds were tested for biological properties.*

Keywords: α,β-unsaturated γ-oxo acids; antimicrobial activities; Michael additions

Previous communications reported the Michael reaction of methyl β-benzoylacrylate[1] with nitromethane, cinnamylidene aniline,[2] dichlorochalkone,[3] arylidene malononitrile,[4] and β-(4-chloro-3-methylbenzoyl)acrylic acid[5] and active methylene compounds. The only few examples dealing with the Michael cycloaddition reaction of α,β-unsaturated γ-oxo carboxylic acids to the compounds containing active methylene groups, prompted the authors to extend the previous studies[1–5] to include the title compounds in order to obtain more precise information about the course of the reaction.

It has been found that in these acids the polarization of the olefinic double bond by a ketone group outweights that caused by the

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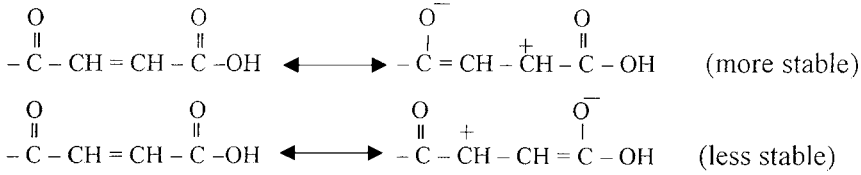
carboxyl group, the keto group giving a more stable carbenium ion than the carboxyl group,[6] that is, the α-carbon atom accepts the nucleophiles (donor in Michael condensation) more readily than the β-carbon atom.



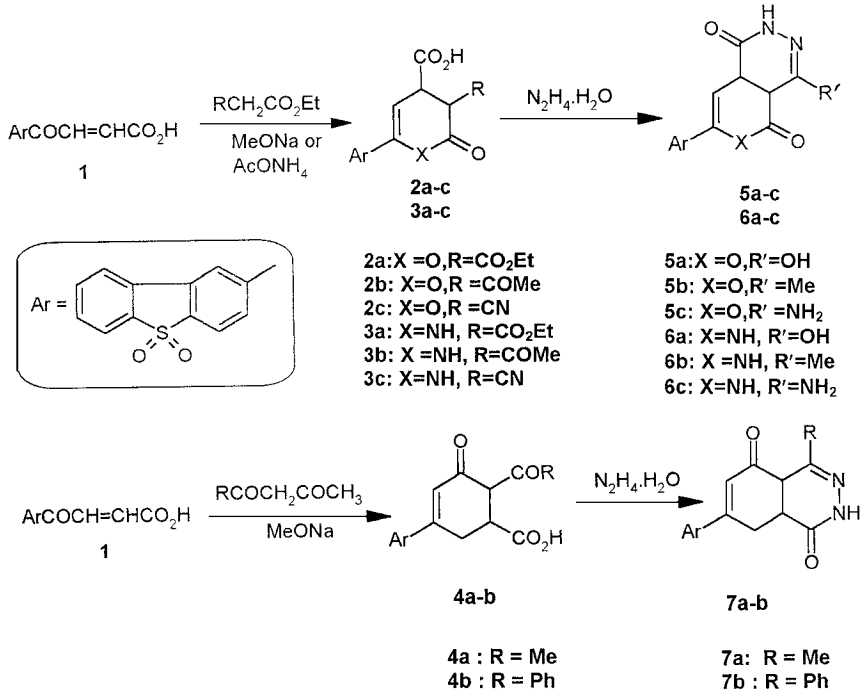
In continuation of our studies,[6–8] this work investigates the Michael addition reaction of 4-(5,5-dioxodibenzothiophen-2-yl)-4-oxo-2-butenoic acid (**1**) with active methylene compounds, which was studied in order to ascertain the mode of addition of activated methylene compounds, since **1** could behave as an α,β-unsaturated acid or as an α,β-unsaturated ketone. Thus, it was found in the present work that acid **1** underwent Michael condensation with diethyl malonate, ethyl acetoacetate and/or ethyl cyanoacetate by heating at 165°C in the presence of sodium methoxide to afford 6-(5,5-dioxodibenzothiophen-2-yl)-3-ethoxycarbonyl (acetyl or cyano)-2-oxo-2H,3H, 4H-pyran-4-carboxylic acids (**2a–c**). However, when the reaction was carried out in the presence of ammonium acetate 6-(5,5-dioxodibenzothiophen-2-yl)-3-ethoxycarbonyl (acetyl or cyano)-2-oxo-1H,2H,3H,4H-pyridin-4-carboxylic acids (**3a–c**) were obtained as the sole products. The formation of **2a–c** and **3a–c** presumably involves the attack of the anion derived from the active methylene compounds at the α-carbon in the acid **1** followed by cyclization to give the desired Michael adducts. Also, **3a–c** can be obtained alternatively via heating compounds **2a–c** with ammonium acetate, which were identified by m.p. and mixed m.p. determination.

Similarly, when the acid **1** was fused with acetylacetone and/or benzoylacetone in the presence of sodium methoxide, 6-acetyl (or benzoyl)-3-(5,5-dioxodibenzothiophen-2-yl)-5-oxo-3-cyclohexene-1-carboxylic acids (**4a–b**) were obtained as the sole products.

On the other hand, our literature survey has revealed that both 6-acetyl-3-(p-chlorophenyl- or p-methoxyphenyl)-5-oxo-3-cyclohexene-1-carboxylic acid and the corresponding cinnamoyl cyclohexenone carboxylic acid derivatives behave as 1,3-diketones when allowed to react with nitrogen nucleophiles[9] in boiling ethanol or acetic acid. In this study we wanted to find out whether the Michael adducts **2a–c**, **3a–c**, and **4a–b** behave as 1,3-diketones or as keto acids when allowed to react with hydrazine hydrate.

Thus, the condensation of Michael adducts **2a–c**, **3a–c**, and **4a–b** with hydrazine hydrate in boiling ethanol afforded 7-(5,5-dioxodibenzothiophen-2-yl)-1,4,5-trioxo-1H,2H,3H,4H,4aH,5H,8aH-pyrano[3,4-d]pyridazine (**5a**), 7-(5,5-dioxodibenzothiophen-2-yl)-1,5-dioxo-4-methyl (or amino)-1H,2H,4aH,5H,8aH-pyrano[3,4-d]pyridazines (**5b–c**), 7-(5,5-dioxodibenzothiophen-2-yl)-1,4,5-trioxo-1H,2H,3H,4H,4aH,5H,6H,8aH-pyrido[3,4-d]pyridazine (**6a**), 7-(5,5-dioxodibenzothiophen-2-yl)-1,5-dioxo-4-methyl (or amino)-1H,2H,4aH,5H,6H,8aH-pyrido[3,4-d]-pyridazines (**6b–c**), and 6-(5,5-dioxodibenzothiophen-2-yl)-4,8-dioxo-1-methyl (or phenyl)-3H,4H,4aH,5H,8H,8aH-phthalazines (**7a–b**) respectively, which were found to behave as keto acids to furnish a thermodynamically more stable compound rather than as 1,3-diketones in their mode of condensation with hydrazine hydrate. This was supported by their analytical and spectral data.

The structural assignments of all the compounds (Scheme 1) were based on elemental analyses (Table I) and characteristic IR, ^{1}H NMR, and mass spectral data (Table II).



SCHEME 1

TABLE I Analytical Data of Various Compounds Synthesized

Comp. no.	m.p.[a] (°C)	Yield (%)	Mol. formula (mol. wt.)	Calcd (found) (%) C	H	N
2a	160–162	65	$C_{21}H_{16}O_8S$ (428.41)	58.87 (58.74	3.76 3.82	— —)
2b	210–212	63	$C_{20}H_{14}O_7S$ (398.38)	60.29 (60.40	3.54 3.62	— —)
2c	190–192	61	$C_{19}H_{11}NO_6S$ (381.36)	59.84 (60.04	2.90 2.74	3.67 3.68)
3a	166–168	72	$C_{21}H_{17}NO_7S$ (427.43)	59.01 (59.23	4.00 4.28	3.27 3.51)
3b	192–193	75	$C_{20}H_{15}NO_6S$ (397.40)	60.44 (60.40	3.80 3.88	3.52 3.39)
3c	201–203	71	$C_{19}H_{12}N_2O_5S$ (380.37)	59.99 (60.11	3.17 3.34	7.36 7.58)
4a	253–255	68	$C_{21}H_{16}O_6S$ (396.41)	63.62 (63.52	4.06 4.24	— —)
4b	226–228	70	$C_{26}H_{18}O_6S$ (458.48)	68.11 (68.34	3.95 4.10	— —)
5a	181–183	62	$C_{19}H_{12}N_2O_6S$ (396.37)	57.57 (57.72	3.05 3.14	7.06 7.31)
5b	222–224	59	$C_{20}H_{14}N_2O_5S$ (394.40)	60.90 (60.80	3.57 3.72	7.10 7.35)
5c	230–232	65	$C_{19}H_{13}N_3O_5S$ (395.39)	57.71 (57.46	3.31 3.50	10.62 10.84)
6a	208–210	73	$C_{19}H_{13}N_3O_5S$ (395.39)	57.71 (57.50	3.31 3.43	10.62 10.54)
6b	238–240	70	$C_{20}H_{15}N_3O_4S$ (393.42)	61.05 (61.28	3.84 3.91	10.68 10.48)
6c	220–222	68	$C_{19}H_{14}N_4O_4S$ (394.40)	57.86 (57.69	3.57 3.81	14.20 14.14)
7a	188–190	60	$C_{21}H_{16}N_2O_4S$ (392.43)	64.27 (64.44	4.10 4.03	7.13 7.25)
7b	160–162	70	$C_{26}H_{18}N_2O_4S$ (454.50)	68.70 (68.45	3.99 4.22	6.16 6.42)

[a]All compounds were recrystallized from ethanol except for **3b**, **3c**, and **6a** which were recrystallized from benzene.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Pye-Unicam Sp-1200 spectrophotometer and ^{1}H NMR spectra in DMSO on a JOEL Fx 90 Q9 MHz (Fourier transform NMR spectrometer) using TMS as internal reference (chemical shifts are expressed as δ, ppm). Mass spectra were recorded on an HP Model MS 5988 spectrometer and microanalytical

TABLE II Spectral Data of Compound **2a–7b**

Comp. no.	IR (KBr) (cm^{-1})	^1H NMR (DMSO) δ/ppm[a]	MS (70 eV) m/z (%)
2a	3400–3300 (OH), 1745–1680 (CO, α-pyrone, ester, and acid), 1630 (C═C)	1.21 (t, J = 7.1 Hz, 3H, CH_3), 3.39–3.81 (m, 2H, methine-H), 4.20 (q, J = 7.1 Hz, 2H, CH_2), 5.92 (d, J = 2.3 Hz, 1H, olefinic-H), 7.18–7.91 (m, 7H, Ar—H), 11.53 (s, 1H, COOH)	428 (M^+, 1.7), 337 (1.54), 311 (2.3), 216 (100), 215 (5.12), 166 (2.86), 151 (15.99), 140 (5.77), 122 (4.8), 96 (15.31), 76 (16.09), 75 (20.74), 52 (9.03)
2b	3450–3320 (OH), 1748–1670 (CO, α-pyrone, acid, and ketone), 1625 (C═C)	2.23 (s, 3H, $COCH_3$), 3.30–3.70 (m, 2H, methine-H), 6.24 (d, J = 2.4 Hz, 1H, olefinic-H), 6.92–7.81 (m, 7H, Ar—H), 12.23 (s, 1H, COOH)	
2c	3460–3340 (OH), 2240 (C≡N), 1745–1718 (CO, α-pyrone, and acid), 1622 (C═C)	2.64 (q, J = 2.7 Hz, 1H, CHCOOH), 3.17 (d, J = 2.7 Hz, 1H, CHCN), 5.93 (d, J = 2.4 Hz, 1H, olefinic-H), 6.84–7.88 (m, 7H, Ar—H), 11.87 (s, 1H, COOH)	
3a	3470–3180 (OH and NH), 1731–1666 (CO, ester, acid, and amide), 1617 (C═C), 1607 (C═N)	1.11 (t, J = 7.1 Hz, 3H, CH_3), 3.28–3.72 (m 2H, methine-H), 4.12 (q, J = 7.1 Hz, 2H, CH_2), 5.63 (d, J = 2.1 Hz, 1H, olefinic-H), 6.93–7.95 (m, 7H, Ar—H), 8.56 (br s, 1H, NHCO), 11.60 (s, 1H, COOH)	428 (M^++1, 0.14), 216 (100), 215 (3.38), 212 (0.15), 183 (0.93), 95 (3.77), 76 (8.95)
3b	3360–3140 (OH and NH), 1719–1669 (CO, acid, ketone, and amide), 1624 (C═C), 1595 (C═N)	2.34 (s, 3H, $COCH_3$), 3.46–3.94 (m, 2H, methine-H), 5.74 (d, J = 2.3 Hz, 1H, olefinic-H), 6.80–7.92 (m, 7H, Ar—H), 8.45 (br s, 1H, NHCO), 12.20 (s, 1H, COOH)	397 (M^+, 0.01), 216 (100), 215 (12.89), 182 (2.43), 167 (1.20), 95 (3.40), 78 (3.12)
3c	3475–3178 (OH and NH), 2235 (C≡N), 1720–1670 (CO, acid, amide), 1625 (C═C), 1610 (C═N)	2.66 (q, J = 2.7 Hz, 1H, CHCOOH), 3.22 (d, J = 2.7 Hz, 1H, CHCN), 5.81 (d, J = 2.3 Hz, 1H, olefinic-H), 6.84–7.96 (m, 7H, Ar—H), 8.60 (br s, 1H, NHCO), 12.45 (s, 1H, COOH)	

(Continued on next page)

TABLE II Spectral Data of Compound **2a–7b** *(Continued)*

Comp. no.	IR (KBr) (cm^{-1})	^1H NMR (DMSO) δ/ppm[a]	MS (70 eV) m/z (%)
4a	3455–3220 (OH), 1722–1680 (CO, acid, cyclic and acyclic ketone), 1620 (C═C)	2.14 (d, J = 13.2 Hz, 2H, CH_2), 2.34 (s, 3H, $COCH_3$), 3.07–3.53 (m, 2H, methine-H), 6.13 (s, 1H, olefinic-H), 6.91–7.92 (m, 7H, Ar—H), 11.75 (s, 1H, COOH)	396 (M^+, 0.09), 216 (100), 181 (0.48), 138 (2.61), 137 (3.39), 122 (1.48)
4b	3450–3230 (OH), 1725–1680 (CO, acid, cyclic and acyclic ketone), 1620 (C═C)	2.19 (d, J = 13.2 Hz, 2H, CH_2), 3.21–3.59 (m, 2H, methine-H), 6.28 (s, 1H, olefinic-H), 6.81–7.94 (m, 12 H, Ar—H), 12.35 (s, 1H, COOH)	
5a	3440–3190 (OH and NH), 1746–1731 (CO, α-pyrone), 1670–1655 (CO, amide), 1625 (C═C), 1595 (C═N)	3.29–3.71 (m, 2H, methine-H), 5.86 (d, J = 2.2 Hz, 1H, olefinic-H), 6.84–7.92 (m, 7H, Ar—H), 8.9 (br s, 1H, NHCO)	
5b	3460–3170 (OH and NH), 1748–1730 (CO, α-pyrone), 1670–1650 (CO, amide), 1628 (C═C), 1598 (C═N)	1.92 (s, 3H, CH_3), 2.98–3.42 (m, 2H, methine-H), 5.81 (d, J = 2.2 Hz, 1H, olefinic-H), 6.93–7.84 (m, 7H, Ar—H), 8.98 (br s, 1H, NHCO)	
5c	3470–3210 (OH, NH_2 and NH), 1745–1729 (CO, α-pyrone), 1675–1660 (CO, amide), 1624 (C═C), 1580 (C═N)	3.28–3.72 (m, 2H, methine-H), 5.24 (s, 2H, NH_2), 5.86 (d, J = 2.2 Hz, 1H, olefinic-H), 6.92–7.93 (m, 7H, Ar—H), 8.95 (br s, 1H, NHCO)	
6a	3460–3170 (OH and NH), 1676–1648 (CO, amide), 1625 (C═C), 1604 (C═N)	3.19–3.61 (m, 2H, methine-H), 5.99 (d, J = 2.2 Hz, 1H, olefinic-H), 6.81–7.92 (m, 7H, Ar—H), 8.22–8.89 (br s, 3H, 3x NHCO)	
6b	3420–3210 (OH and NH), 1678–1645 (CO, amide), 1624 (C═C), 1601 (C═N)	1.96 (s, 3H, CH_3), 3.29–3.71 (m, 2H, methine-H), 5.89 (d, J = 2.2 Hz, 1H, olefinic-H), 6.87–7.89 (m, 7H, Ar—H), 8.26–9.06 (br s, 2H, 2x NHCO)	

TABLE II Spectral Data of Compound **2a–7b** *(Continued)*

Comp. no.	IR (KBr) (cm^{-1})	^{1}H NMR (DMSO) δ/ppm[a]	MS (70 eV) m/z (%)
6c	3480–3210 (OH, NH_2 and NH), 1680–1640 (CO, amide), 1630 (C═C), 1606 (C═N)	3.21–3.59 (m, 2H, methine-H), 5.14 (s, 2H, NH_2), 5.91 (d, J = 2.2 Hz, 1H, olefinic-H), 6.92–7.91 (m, 7H, Ar—H), 8.43–9.11 (br s, 2H, 2x NHCO)	396 (M^+ + 2, 0.72), 352 (0.79), 216 (66.25), 215 (5.23), 181 (5.88), 179 (3.61), 137 (16.43), 109 (19.98), 95 (31.94), 55 (100)
7a	3420–3175 (OH and NH), 1690–1662 (CO, ketone, and amide), 1626 (C═C), 1608 (C═N)	1.80 (s, 3H, CH_3), 2.12 (d, J = 13.2 Hz, 2H, CH_2), 2.82–3.18 (m, 2H, methine-H), 6.24 (s, 1H, olefinic-H), 6.94–7.97 (m, 7H, Ar—H), 8.83 (br s, 1H, NHCO)	
7b	3440–3250 (OH and NH), 1685–1665 (CO, ketone, and amide), 1622 (C═C), 1606 (C═N)	2.16 (d, J = 13.2 Hz, 2H, CH_2), 3.22–3.58 (m, 2H, methine-H), 6.17 (s, 1H, olefinic-H), 6.88–7.94 (m, 12H, Ar—H), 8.55 (br s, 1H, NHCO)	

[a]All NH and OH signals were exchangeable with deuterium oxide.

data were obtained from the Microanalytical Center at Cario University.

6-(5,5-Dioxodibenzothiophen-2-yl)-3-ethoxycarbonyl (acetyl or cyano)-2-oxo-2H,3H,4H-pyran-4-carboxylic Acids (2a–c) and 6-acetyl (or Benzoyl)-3-(5,5-dioxodibenzothiophen-2-yl)-5-oxo-3-cyclohexene-1-carboxylic Acids (4a–b)

A mixture of acid **1** (2.5 g, 8 mmol), the active methylene compounds, namely, diethyl malonate (1.28 g), ethyl acetoacetate (1.04 g), ethyl cyanoacetate (0.9 g), acetylacetone (0.8 g) or benzoylacetone (1.3 g, 8 mmol) and sodium methoxide solution [prepared from Na (0.28 g, 12 mmol) and MeOH (20 mL)] was heated in a sealed tube at 165°C for 6 h. The reaction mixture was poured into water (100 mL), extracted with ether and the aqueous layer acidified with ice-cold diluted hydrochloric acid (100 g/15 mL) and extracted with ether. Slow evaporation of the dried ether extract gave the desired products as solids

which crystallized from an appropriate solvent to give the Michael adducts **2a–c** and **4a–b**.

6-(5,5-Dioxodibenzothiophen-2-yl)-3-ethoxycarbonyl (Acetyl or Cyano)-2-oxo-1H,2H,3H,4H-pyridin-4-carboxylic Acids (3a–c)

They were prepared by the same procedure as described above with the exception that the mixture was fused with ammonium acetate (6.2 g, 80 mmol) instead of sodium methoxide at 170°C for 5 h to give **3a–c**.

Alternative Preparation 3a–c

A mixture of **2a–c** (1.5 mmol) and ammonium acetate (1.15 g, 15 mmol) was fused at 180°C for 4 h. After being cooled, the reaction mixture was poured into water (100 mL) and worked up as above to yield a compound identified to be **3a–c** by melting point and mixed melting point determination.

Reaction of the Michael Adducts with Hydrazine Hydrate

Formation of Compounds 5a–c, 6a–c, and 7a–b

A solution of each of the Michael adducts **2a–c**, **3a–c**, and **4a–b** (2 mmol) in ethanol (30 mL) was treated with hyrazine hydrate (0.1 g, 2 mmol) and the solution was refluxed for 6 h. The solid product formed after concentration and cooling was crystallized from an appropriate solvent to give **5a–c**, **6a–c**, and **7a–b** respectively.

SCREENING FOR ANTIMICROBIAL ACTIVITY

The antimicrobial activities of the synthesized derivatives were determined in vitro by the filter paper disc method.[10] All compounds were tested for activity against gram-positive, gram-negative bacteria, and selected fungi.

The culture medium was normal nutrient agar (NA) supplemented with 1 g of yeast per ml. According to the solubility of the tested compounds, different polar and nonpolar solvents were used, and a good solubility was found in 10% acetone (V/V) for all test compounds. Based on the previous preliminary test, closely spaced test concentrations (500, 250, 125 μg/ml) were selected. A qualitative screen was performed on all compounds while quantitative assays were done on active compounds only. The results are summarized in Table III.

TABLE III Activity (A) and Minimum Inhibitory Concentration (MIC) Calculated as mmol/ml for Compounds **2b–7b**

Comp. no.	Bacillus subtilis		Bacillus cereus		Escherichia coli		Aspergillus niger		Penicillium notatum	
	A[a]	MIC[b]	A	MIC	A	MIC	A	MIC	A	MIC
2b	+	0.62×10^{-3}	+	0.62×10^{-3}	+	0.31×10^{-3}	++	0.62×10^{-3}	+	0.31×10^{-3}
3c	+	0.65×10^{-3}	+++	0.65×10^{-3}	+	0.13×10^{-2}	+	0.13×10^{-2}	+	0.65×10^{-3}
4a	+	0.63×10^{-3}	++	0.31×10^{-3}	+	0.63×10^{-3}	+	0.12×10^{-2}	++	0.63×10^{-3}
5c	++	0.32×10^{-3}	++	0.65×10^{-3}	++	0.65×10^{-3}	+	0.65×10^{-3}	+	0.32×10^{-3}
6b	+++	0.12×10^{-2}	++	0.12×10^{-2}	++	0.63×10^{-3}	+	0.63×10^{-3}	+	0.31×10^{-3}
7b	+	0.27×10^{-3}	+	0.55×10^{-3}	+	0.55×10^{-3}	+	0.11×10^{-2}	+	0.27×10^{-3}

[a]The width of the zone of inhibition indicates the potency of antimicrobial activity.

(−) no antimicrobial activity; (+) weak activity with the diameter of the zone equal to 0.7 cm.; (++) moderate activity with the diameter of the zone equal to 1.3 cm.; (+ + +) marked activity with the diameter of the zone equal to 1.7 cm.

[b]Origin of cultures: Botany Department, Faculty of Science, Benha University, Egypt. The results of control samples were not included in the table; they show negative response.

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