World Applied Sciences Journal 24 (3): 312-319, 2013
ISSN 1818-4952
© IDOSI Publications, 2013
DOI: 10.5829/idosi.wasj.2013.24.03.509

Antimicrobial Susceptibility of Certain Fungal and Bacterial Strains to Dodecanamide and Quinazolinone Derivatives

[1]A.A. Abdalha and [2]A.A.I. Mekawey
[1]Department of Chemistry, Ain Shams University, Abbassia, Cairo, Egypt
[2]Regional center of mycology and Biotechnology, Al-Azhar University, Cairo, Egypt

Submitted: Mar 9, 2013; **Accepted:** Apr 17, 2013; **Published:** Aug 25, 2013

Abstract: The hitherto unknown 6,8-dibromo-2-undecyl-4H-benzo [d] [1,3] oxazin-4-one (2) was synthesized via cyclization of 3,5-dibromo-2-dodoecanamido benzoic acid (1). The benzoxazinone derivative (2) was allowed to react with primary amines as benzylamine, 4-methyl aniline and/or 4-methoxy aniline providing benzamide derivatives (3a-c) respectively. Secondary amines such as piperidine and/or morpholine were subjected to react with (2) to give dodecanamide derivatives (4a) and/or (4b) respectively. On the other hand, aminolysis of (2) with ethanolamine gave a mixture of benzamide derivative (5) and quinazolinone derivative (6). Hydrazinolysis of the benzoxazinone derivative (2) afforded the aminoquinazolinone derivative (7) which was acylated under the influence of acetyl chloride giving the corresponding acetylamino quinazolinone derivative (8). Fusion of (2) with ammonium acetate and/or formamide yielded the quinazolinone derivative (9) which was thiated by using Lawessen's reagent to give the thione derivative (10).

Key words: Benzoxazinone · Quinazolinone · Antimicrobial · MIC

INTRODUCTION

The pronounced biological and pharmacological activities as anticonvalsant [1,2], antihistaminic [3], antihypertensive [4-7], fungicidal [8] and antimicrobial [9] of quinazolinone and amide derivatives have stimulated us to synthesize new compounds of quinazolinone as well as amide derivatives.

RESULTS AND DISCUSSION

The key starting material 6,8-dibromo-2-undecyl-4H-benzo[d][1,3]oxazin-4-one (2) was synthesized via cyclization of 3,5-dibromo-2-dodecanamido benzoic acid (1) by using freshly distilled acetic anhydride. Benzoic acid derivative (1) was obtained by stirring a solution of 3,5-dibromoanthranilic acid with equimolar ratio of lauryl chloride in pyridine as a catalytic base (Scheme 1).

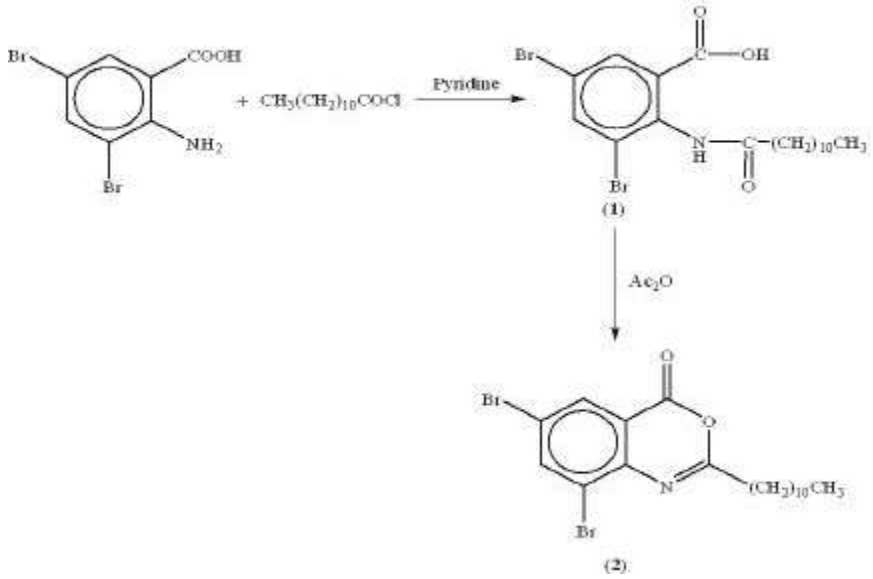
The structure of (2) was established by elemental analysis as well as spectral data (IR, ^{1}H-NMR, MS) and chemically via aminolysis with primary amines such as benzylamine, 4-methyl aniline and/or 4-methoxy aniline to give benzamide derivatives (3a-c) respectively. Also, treatment of oxazine derivative (2) with secondary amines as piperidine and/or morpholine afforded dodecanamide derivatives (4a) and/or (4b) respectively. On the other hand, aminolysis of (2) with bifunctional nucleophile, ethanolamine, yielded a mixture of 3,5-dibromo-2-dodecanamido-N-(2-hydroxyethyl)benzamide (5) and 6,8-dibromo-3-(2-hydroxyethyl)-2-undecylquinazolin-4(3H)-one (6).

Hydrazinolysis of oxazine derivative (2) with hydrazine hydrate in benzene provided 3-amino-6,8-dibromo-2-undecylquinazolin-4(3H)-one (7), whose structure was confirmed by elemental analysis as well as spectral data.

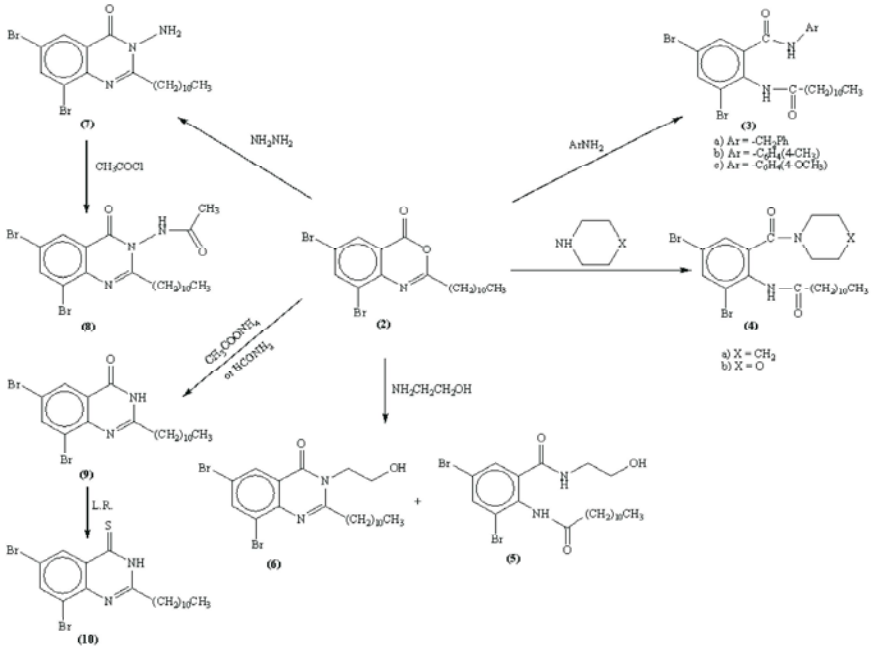
Furthermore, chemical proof is achieved via acetylation with acetic anhydride to yield N-(6,8-dibromo-4-oxo-2-undecylquinazolin-3(4H)-yl)acetamide (8) in fairly good yield. Fusion of (2) with ammonium acetate and/or formamide, afforded 6,8-dibromo-2-undecylquinazolin-4(3H)-one (9), which underwent thiation using Lawessen's reagent to give 6,8-dibromo-2-undecyl quinazo line -4(3H)-thione (10) (Scheme 2).

Experimental: Melting points were measured on an electrothermal melting point apparatus and are uncorrected. Elemental analyses were carried out at the

Corresponding Author: A.A. Abdalha, Department of Chemistry,Tabuk university,Tabuk, KSA.



Scheme 1:



Scheme 2:

Micro-analytical unit, Cairo University. Infrared spectra were measured on a Unicam SP-1200 spectrometer using KBr wafer technique. ^{1}H-NMR spectra were measured in DMSO-d_6 on a varian plus instrument (300 MHz). The mass spectra were determined using HP model MS-5988 at electron energy 70 eV.

3,5-dibromo-2-dodecanamidobenzoic Acid (1): To a solution of 3,5-dibromoanthranilic acid (0.01 mol) in anhydrous pyridine (50 mL), lauryl chloride (0.01 mol) was added dropwise at room temperature with stirring for 30 min; then the reaction mixture was heated on a water bath for 5 h. after cooling, the reaction mixture was poured on ice cold hydrochloric acid. The produced mass was filtered, washed with water, dried and recrystallized to give (1).

6,8-dibromo-2-undecyl-4H-benzo[d][1,3]oxazin-4-one(2): A mixture of (1) (0.01 mol) and acetic anhydride (50 mL) was heated on a water bath for 5 h. The solid

formed after removal of excess acetic anhydride was triturated with petroleum ether 40-60°C and recrystallized to give (2).

N-benzyl-3,5-dibromo-2-dodecanamidobenzamide, 3,5-dibromo-2-dodecan-amido-n-p-tolylbenzamide and 3,5-dibromo-2-dodecanamido-n-(4-meth-oxyphenyl)benzamide (3a-c): A mixture of (2) (0.01 mol) and primary amines, namely benzylamine, 4-methyl aniline and 4-methoxy aniline (0.01 mol) in benzene (30 mL) was refluxed for 3 h. The solid separated after concentration of benzene was filtered and recrystallized form the proper solvent to give (3a-c).

N-(2,4-dibromo-6-(Piperidine-1-carbonyl) phenyld odecanamide (4a) and N-(2,4-dibromo-6-(Morpholine-4-carbonyl)phenyldodecanamide (4b): A mixture of (2) (0.01 mol) and secondary amines, namely piperidine and/or morpholine (0.01 mol) in benzene (30 mL) was refluxed for 5 h. The solid separated after concentration of benzene was filtered and recrystallized form the proper solvent to give (4a and 4b).

3,5-dibromo-2-dodecanamido-n-(2-hydroxyethyl) benzamide (5) and 6,8-dibromo-3-(2-hydroxyethyl)-2-undecylquinazolin-4(3h)-one (6): A mixture of (2) (0.01 mol) and ethanolamine (0.01 mol) in ethanol (30 mL) was refluxed for 4 h. The solid formed after concentration of ethanol was filtered and recrystallized form the proper solvent to give (5) and (6).

3-amino-6,8-dibromo-2-undecylquinazolin-4(3h)-one (7) A mixture of (2) (0.01 mol) and hydrazine hydrate (0.01 mol) in benzene (30 mL) was stirred at room temperature for 2 h. The solid formed after concentration of benzene was filtered and crystallized to give (7).

N-(6,8-dibromo-4-oxo-2-undecylquinazolin-3(4h)-yl) acetamide (8): A mixture of (7) (0.01 mol) and acetyl chloride (30 mL) was refluxed for 6 h. The solid separated after evaporation of acetyl chloride was collected and recrystallized to give (8).

6,8-dibromo-2-undecylquinazolin-4(3h)-one (9)
Method (A): A mixture of (2) (0.01 mol) and ammonium acetate (0.04 mol) was fused at 160°C for 3 h. After cooling, the solid mass formed was triturated with warm water, filtered, washed with water and recrystallized to give (9).

Method (B): A mixture of (2) (0.01 mol) and formamide (30 mL) was heated for 5 h. After cooling, the reaction mixture was poured onto ice cold water, the solid formed was filtered and recrystallized to give (9).

6,8-dibromo- 2- undecylquinazoline-4 (3H) thione (10) A mixture of (9) (0.01 mol) and Lawessen's reagent (0.01 mol) in dry toluene (30 mL) was refluxed for 5 h. The solid separated after concentration of toluene was collected and recrystallized to give (10).

Biological Activity: Rapid emergence of antimicrobial resistance is well documented as a serious problem worldwide. This situation shows that the potencies of prevalent antibacteral and antifungal are decreasing steadily. This situation implies the need for searching new antimicrobial to replace with invalidated ones or use in antimicrobial rotation programs [10,11].

Fungi are gaining importance with increased incidence of chronic, often fatal mycoses in immuno-compromised patients. Fungal infections are caused by eukaryotic organisms and for that reason they generally present more difficult therapeutic problems than do bacterial infections. Although invasive fungal diseases are now more frequent than during the first half of the century, they are still difficult to diagnose clinically. During the latter half of the century, particularly during the past two decades, a number of different classes of antifungal agents have been discovered; there is still a critical need for new antifungal agents to treat life-threatening invasive mycoses [12].

MATERIAL AND METHODS

Culture Media: Two specific media were used for detecting the antimicrobial activity, Malt Extract Agar (MEA) for fungal isolates [Malt extract, 20.0g; Bacteriological Peptone, 5.0g; Agar, 20.0g, the pH was adjusted at 5.4 ± 0.2 at 25 (±2)°C] while, Nutrient agar medium was used for bacterial growth [Beef Extract, 3.0g; Bacteriological Peptone, 5.0g; Agar, 20.0g, the pH was adjusted at 6.2 ± 0.2 at 25 (±2)°C]. Each medium was prepared by dissolving the solid ingredients in 1 liter of cold distilled water and then heating to 60-70 °C with stirring. Media were sterilized by autoclaving at 121°C (1.5 atm.) for 15-20 minutes [13].

2. Micro-organisms Isolates Used: four clinical fungal strains employed for this investigation including four filamentous fungi (*Aspergillus flavus*, *Penicillium*

expansum and *Syncephalastrum racemosum*) and one unicellular fungi (*Candida albicans*) and two gram positive (*Staphylococcus aureus, Bacillus subtilis*), two gram negative (*Klebsiella pneumonia* and *Salmonella typhi)* bacteria. All strains were kindly provided from culture collection of the Regional Center for Mycology and Biotechnology (RCMB), AL-Azhar University.

Antimicrobial Assays: By diffusion agar technique, the antifungal and antibacterial potentialities against several species were expressed as the measurement of diameter of their inhibition zone. Hole-plate diffusion method was used; Six equidistant (1 cm diameter) holes were made using sterile cork borer in Malt Extract Agar and Nutrient agar sterile plates (10x 10 cm), which had previously been seeded with tested fungal and bacterial isolates. Holes were filled with 100 µL of three different concentrations of samples 5, 25 and 1 mg/ml of each synthesized compounds after complete dissolved in benzene solvent. Control holes were filled with benzene. Plates were left in a cooled incubator at 4 (±2)°C for one hour and then incubated at 37 (±2) °C for bacterial isolates and incubated at 28 (±2) °C for fungal isolates used. Inhibition zones developed due to active ingredients were measured after 24-48 hours of incubation time [14]. Terbinafin was used as a standard antifungal agent while Amoxicilli was used as a standard antibacterial agent.

Minimum Inhibitory Concentration (MIC) Assays: MIC determination was performed by a serial dilution technique described by Irobi *et al*. [15]. Appling benzene of synthesized compounds started with a maximum concentration of 5000 µg/ml and then reduced it by successive two - fold dilutions of that stock solution using a calibrated micropipette. MIC of the most active sample showed antimicrobial potency was determinate and carried out by inoculation of their serial dilutions with test organisms and measurement of inhibition zones using diffusion agar technique. MIC was expressed as the lowest concentration inhibiting test organisms growth. Samples that showed no antimicrobial activity at concentrations of 5 mg/ml were considered in active [16] and [17].

RESULTS AND DISCUSSION

The results of the compounds of preliminary antimicrobial testing are shown in Table 1 (A and B) and Figure 1. The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. Susceptibilities of fungal and bacterial isolates to different chemical compounds were investigated by measuring their inhibitory effect on the growth, compared to the solvent used.

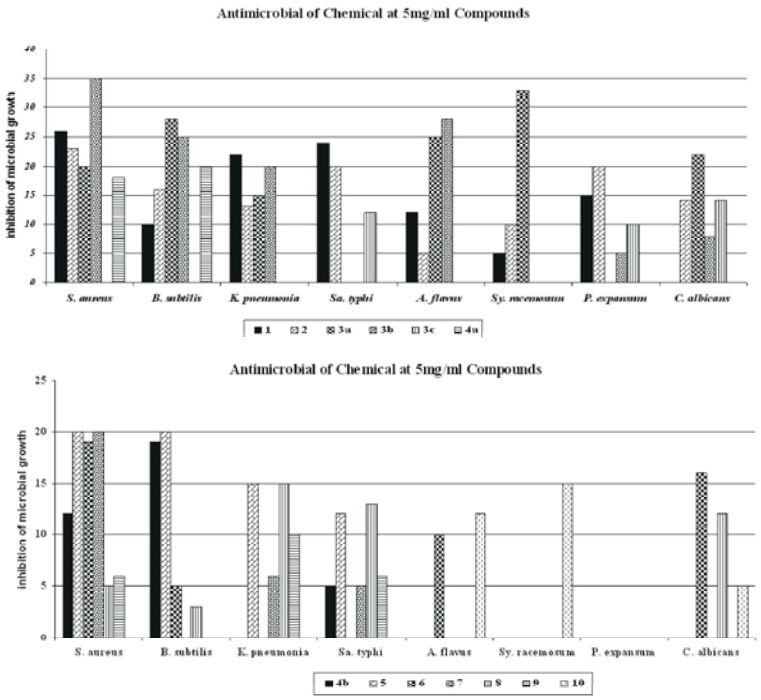


Fig. 1: *In vitro* antiimicrobial susceptibility of pathogenic microorganisms strains to synthesized compounds at 5 mg/ml

Table 1: Characterization data of prepared compounds.

Compound No.	M.P.°C (Color)	Yield %, Solvent of cryst.	Mol. Formula (M.Wt.)	Analysis Cal/Found C%	H%	N%
1	125-27 (colorless)	80	$C_{19}H_{27}NO_3Br_2$ (477.23)	47.82 5.70	47.84 2.93	5.69 2.91
2	80-83 (colorless)	75	$C_{19}H_{25}NO_2Br_2$ (459.21)	49.69 5.47	49.71 3.05	5.48 3.03
3a	185-87 (colorless)	60	$C_{26}H_{34}N_2O_2Br_2$ (566.35)	55.14 6.04	55.15 4.94	6.04 4.93
3b	238-40 (colorless)	55	$C_{26}H_{34}N_2O_2Br_2$ (566.35)	55.14 6.05	55.15 4.94	6.04 4.95
3c	241-43 (colorless)	65	$C_{26}H_{34}N_2O_3Br_2$ (582.35)	53.62 5.88	53.60 4.81	5.87 4.80
a	155-57 (colorless)	75	$C_{24}H_{34}N_2O_2Br_2$ (544.34)	52.95 6.64	52.93 5.14	6.65 5.14
4b	90-93 (colorless)	75	$C_{23}H_{34}N_2O_3Br_2$ (546.32)	50.56 6.25	50.57 5.12	6.26 5.13
5	158-60 (colorless)	80	$C_{21}H_{32}N_2O_3Br_2$ (520.28)	48.48 6.19	48.49 5.38	6.19 5.37
6	100-02 (colorless)	60	$C_{21}H_{30}N_2O_2Br_2$ (502.27)	50.21 6.03	50.23 5.57	6.01 5.58
7	125-27 (colorless)	55	$C_{19}H_{27}N_3OBr_2$ (473.23)	48.22 5.73	48.23 8.87	5.74 8.88
8	118-20 (colorless)	65	$C_{21}H_{29}N_3O_2Br_2$ (515.27)	48.95 5.66	48.97 8.15	5.66 8.14
9	158-60 (colorless)	50	$C_{19}H_{26}N_2OBr_2$ (458.33)	49.79 5.70	49.81 6.11	5.71 6.11
10	138-40 (pale yellow)	70	$C_{19}H_{26}N_2SBr_2$ (474.28)	48.11 5.53	48.12 5.90	5.52 5.92

Table 2: ^{1}H-NMR, MS and IR data of prepared compounds.

Compound No.	^{1}H-NMR (δ, ppm)	MS (m/z), %	IR, cm^{-1} OH	NH	C=O
1	13.1 (s, 1H), 9.6 (s, 1H), 8.11 (d, 1H), 7.84 (d, 1H), 2.28 (t, 2H), 1.56-1.24 (m, 18H), 0.84 (t, 3H).	[M - 17] 460 (18%), 371 (100%), 295 (65%), 74 (47%), 55 (64%).	3268	3182	1697, 1665
2	8.37 (d, 1H), 7.68 (d, 1H), 2.37 (t, 2H), 1.73 - 1.27 (m, 18H), 0.89 (t, 3H)	-	-	-	1775
3a	8.82 (br, 2H), 8.03 (d, 1H), 7.66 (d, 1H), 7.32 - 7.28 (m, 5H), 4.40 (d, 2H), 2.52 (t, 2H), 1.88 - 1.26 (m, 18H), 0.87 (t, 3H)	[M - 106] 460 (3%), 421 (3%), 408 (11%), 384 (9%), 106 (70%), 91 (100%), 55 (25%)	-	3267	1666, 1639
3b	10.14 (s, 1H), 9.63 (s, 1H), 8.06 (d, 1H), 7.72 (d, 1H), 7.55 (d, 2H), 7.12 (d, 2H), 3.24 (s, 3H), 2.49 (t, 2H), 1.95 - 1.23 (m, 18H), 0.84 (t, 3H)	[M - 106] 460 (3%), 408 (4%),384 (4%), 107 (100%), 106 (16%), 55 (9%)	-	3263	1670, 1643
3c	10.15 (br, 1H), 9.76 (br, 1H), 8.07 (d, 1H), 7.74 (d, 1H), 7.58 (d, 2H), 6.89 (d, 2H), 3.75 (s, 3H), 2.51 (t, 2H), 1.97 - 1.24 (m, 18H), 0.87 (t, 3H	[M - 122] 460 (7%), 409 (6%),383 (1%), 123 (100%), 108 (14%), 55 (12%)	-	3260	1668, 1643
4a	9.78 (br, 1H), 8.14 (d, 1H), 7.86 (d, 1H), 3.58 - 3.37 (br, 4H), 2.5 (t, 2H), 2.29 - 1.27 (m, 24H), 0.88 (t, 3H)	[M + 2] 546 (5.5%), 544 (2%), 460 (30%), 295 (47%), 84 (7%), 55 (100%)	-	3277	1702, 1660
4b	9.74 (s, 1H), 8.0 (d, 1H), 7.62 (d, 1H), 3.69 - 3.18 (m, 8H), 2.30 (t, 2H), 1.57 - 1.26 (m, 18H), 0.85 (t, 3H)	[M + 2] 548 (6%), 546 (4%), 460 (32%), 362 (14%), 278 (13%), 87 (100%), 55 (38%)	-	3231	1688, 1620

Table 2: Continue

Compound No.	^{1}H-NMR (δ, ppm)	MS (m/z), %	IR, cm^{-1} OH	NH	C=O
5	8.18 (br, 2H), 7.99 (d, 1H), 7.62 (d, 1H), 3.65 (br, 1H), 3.47-3.40 (m, 4H), 2.5 (t, 2H), 2.2 - 1.25 (m, 18H), 0.83 (t, 3H)	[M$^+$] 520 (4.5%), 505 (6%), 459 (23%), 319 (100%), 278 (14%), 55 (46%)	3350	3271	1667, 1643
6	8.35 (d, 1H), 8.20 (d, 1H), 5.00 (br, 1H), 4.16 (br, 2H), 3.67 (t, 2H), 2.52 (t, 2H), 1.82 - 1.26 (m, 18H), 0.87 (t, 3H)	[M$^+$ - 43] 459 (26%), 319 (100%), 55 (38.5%)	3517	-	1657
7	8.30 (d, 1H), 8.18 (d, 1H), 5.78 (s, 2H), 2.95 (t, 2H), 1.82 - 1.24 (m, 18H), 0.83 (t, 3H)	[M + 2] 475 (3%), 473 (4%),333 (100%), 319 (2.5%), 304 (10%), 55 (33%)	-	3283	1679
8	9.98 (br, 1H), 8.38 (d, 1H), 8.19 (d, 1H), 2.75 - 2.68 (m, 5H), 2.13 - 1.24 (m, 18H), 0.82 (t, 3H)	[M + 2] 517 (15%), 515 (18%), 474 (9.5%), 460 (3%), 459 (13%), 375 (100%), 332 (51%), 55 (77%)	-	3333	1704, 1682
9	12.50 (br, 1H), 8.30 (d, 1H), 8.16 (d, 1H), 2.52 (t, 2H), 1.75 - 1.24 (m, 18H), 0.86 (t, 3H)	[M + 2] 460 (6%), 458 (7%), 387 (9%), 373 (13%), 331 (44.5%), 318 (100%), 55 (89%)	-	3159	1685
10	11.90 (br, 1H), 8.25 (d, 1H), 8.10 (d, 1H), 2.50 (t, 2H), 1.72 - 1.21 (m, 18H), 0.84 (t, 3H)	[M + 2] 476 (20%), 474 (19%), 403 (12%), 334 (100%), 55 (89%)	-	3170	-

Table 3 (A): *In vitro* antimicrobial susceptibility of certain fungal and bacterial strains to synthesized compounds at 5, 2.5 and 1mg/ml concentration. Data are expressed as mean diameter of inhibition growth (mm)

	Sample concentration																	
	1			2			3a			3b			3c			4a		
	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
Microorganisms	--------mg/ml-----			-------mg/ml------			-----mg/ml----			-------mg/ml-----			-----mg/ml------			-------mg/ml-----		
Staphylococcus aureus	26	18	05	23	15	10	20	12	06	35	29	20	00	00	00	18	10	02
Bacillus subtilis	10	00	00	16	05	00	28	20	12	25	18	09	00	00	00	20	13	00
Klebsiella pneumonia	22	10	00	13	09	05	15	16	10	20	12	03	00	00	00	00	00	00
Salmonella typhi	24	16	00	20	10	00	00	00	00	00	00	00	12	04	00	00	00	00
Aspergillus flavus	12	05	00	05	00	00	25	19	10	28	20	12	00	00	00	00	00	00
Syncephalastru racemosum	05	00	00	10	00	00	33	20	08	00	00	00	00	00	00	00	00	00
Penicillium expansum	15	06	00	20	15	08	00	00	00	05	00	00	10	03	00	00	00	00
Candida albicans	00	00	00	14	05	00	22	13	00	08	00	00	14	07	00	00	00	00

Table 3(B): *In vitro* antimicrobial susceptibility of certain fungal and bacterial strains to synthesized compounds at 5, 2.5 and 1mg/ml concentration. Data are expressed as mean diameter of inhibition growth (mm)

	Sample concentration																				
	4b			5			6			7			8			9			10		
	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
Microorganisms	----mg/ml----			-----mg/ml-----			----mg/ml----			-----mg/ml-----			-----mg/ml-----			-----mg/ml----			-----mg/ml----		
Staphylococcus aureus	12	06	00	20	12	06	19	11	03	20	10	00	05	00	00	06	00	00	00	00	00
Bacillus subtilis	19	10	03	20	15	08	05	00	00	00	00	00	03	00	00	00	00	00	00	00	00
Klebsiella pneumonia	00	00	00	15	08	04	00	00	00	06	02	00	15	10	06	10	00	00	00	00	00
Salmonella typhi	05	00	00	12	05	00	00	00	00	05	00	00	13	04	00	06	00	00	00	00	00
Aspergillus flavus	00	00	00	00	00	00	10	05	00	00	00	00	00	00	00	00	00	00	12	08	03
Syncephalastrum racemosum	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	15	00	00
Penicillium expansum	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00
Candida albicans	00	00	00	00	00	00	16	00	00	00	00	00	12	08	03	00	00	00	05	00	00

Table 4: MIC of [3a] and[3b] compounds

	MIC		
Organisms	3a compound	3b compound	Std.
A.flavus	50	25	50 (Grisofulvin)
S. aureus	250	75	100 (Amoxicilline)

In general, most of microorganisms used in this study showed high susceptibilities to inhibited by [3a] and [3b] compounds. However, results obtained from the present study recorded remarkable difference in the antibacterial effect (gram positive exhibited most sensitive to thesis compounds than gram negative), the inhibition zones of bacterial growth ranged from 35mm against *Staphylococcus aureus* by [3b] compound at 5 mg/ml followed by 28 mm inhibition against *Bacillus subtilis* at the concentration of [3a] compounds. On the other hands, the minimum inhibition was observed against *Klebsiella pneumonia* (3 mm inhibition) at 1 mg/ml of [3b] compound (Table 3 "A").

Also great antifungal potency was observed by [3a] and [3b] compounds, where 33 mm inhibition was observed against *Syncephalastrum racemosum* at 5mg/ml of [3a] compound while 28 mm inhibition was recorded against *Aspergillus flavus* at 5mg/ml of [3b] compounds (Figure 1 "A").

In addition, data in table (3) reveal that gram positive bacteria were highly susceptible to the other compounds tested where *Staphylococcus aureus* was the most susceptible strain against [1, 2] compounds (26 and 23 mm inhibition of growth at 5mg/ml, respectively), while *Bacillus subtilis* showed little effect against [4a] compound at 1mg/ml concentration (2mm inhibition was observed). On contrast, gram-negative bacteria exhibited great ability to resist the effect of chemical compounds, however, the present study did not agree with the results of Bakr *et al*. [18] who approved that the inhibitory activity of chemical (benzofuran) compounds against the Gram-negative bacteria was higher than that of the Gram-positive bacteria.

Sample [2] showed excellent potency to act as antifungal agent where it recorded high activity against all fungal isolates (inhibitory zone varied from 20 mm against *Penicillium expansum* to 5 mm aganist *A. flavus* at the sam concentration (5mg/ml), respectively) while [4a, 4b,] [5,7, 9] compounds did not exhibited any ability to inhibit the growth of any fungal isolated used figure 1(A and B) while all bacterial isolates used exhibited great ability to resist all concentrations of [3c] and [10] compounds (00 inhibition)

[3a, 3b] compounds had great ability to inhibit most fungal and bacterial isolated so the minimum inhibitory concentration (MIC) of this compounds was carried out against the most sensitive one fungal and other bacterial strains (*A. flavus* and *Staphylococcus aureus*). MIC of compound [3a] against *A. flavus* and *staphylococcus aureus* were 250 and 50µg/ml, respectively, which is equal to Griseofulvin and higher than Amoxicilline while MIC of compound [3b] against *A. flavus* and *staphylococcus aureus* were 25 and 75µg/ml, respectively, which is less than that of Griseofulvin and less than Amoxicilline as reference drugs as depicted in Table (4).

REFERENCES

1. Erusalimsky, J. and R. Franklin, 2002. Experimental Hematology, 30: 625-626.
2. Farghaly, A.M., R. Soliman, M.A. Khalil, A.A. Bekhit and A. El-Din, 2002. Bollettino Chimico Farmaceutico, 141: 372-378.
3. Blackburn, C., M. LaMorche and J. Brown, 2006. Bioorg. and Med. Chem. Lett., 16(10): 2621
4. El-Helby, A., 1995. Egypt Phar. Sci., 36: 287.
5. El-Khamry, A.A., S. El-Nagdy, M.M. Habashy and F.A. El-Bassiouny, 1989. Pharmazie, 44: 312.
6. Ossman, A.E. and S.E. Barakat, 1994. Sauidi Pharm. J., 2: 21.
7. Madkour, H.M., S.A. Shiba, H.M. Sayed and A.A. Hamed, 2001. Sulfur Letters, 24: 151.
8. Alyaa, A.S., A.E. AbdelMomen, A.S. Sayed and A.A. Abdelaal, 2000. Archiv. Der Pharmazie, 333: 355.
9. Ibrahim, S., A. Abdelhalim, Y. Gaber, S. El-Edfawy and R. Abdelrahman, 1997. J. Chem. Res. Synop., 5: 154.l
10. Barbara, D.J. and E. Clewes, 2003. Molecular Plant Pathology, 4(4): 297-305.
11. Shahghasi, A., G.H. Shahidi, M.H. Fooladi and M.J. Mahdari, 2004. Biotechnology, 3(2): 126-130.
12. Walsh, T.J., 1992. Invasive fungal infections: problems and challenges in developing new antifungal compounds. In emerging targets in antibacterial and antifungal chemotherapy (Sutcliffe, J. and Georgopapadakou, N.H. Eds), pp: 349-73. Chapman and Hall, New York,
13. Atlas, R.M., 1993. Handbook of Microbiology Media pp: 278, 538, 785.
14. Abdel-Kader, H.A. and S.R. Seddkey, 1995. Assiut Veterinary Medical Journal, 34: 67.

15. Irobi, O.N., M. Moo-Young and W.A. Anderson, 1996. Int. J. Pharmacog, 34: 87-90.
16. Urzua, A., M. Caroli, L. Vasquea, L. Mendoza, M. Wilkens and E. Tojo, 1998. J. Ethnopharmacology, 62: 251-254.
17. Adedaya, O., W.A. Anderson, M.M. Young and D.O. Kalawole, 1999. Pharmaceutical Biology, 34(5): 369-374.
18. Bakr, F., A. Abdel-Wahab, A. Hatem, A. Abdel-Aziz and M. Essam, 2008. European Journal of Medicinal Chemistry, XXX: 1-4. 0