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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF CERTAIN NEW 1,2,4-TRIAZOLE AND p-AMINOBENZOIC ACID DERIVATIVES

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ABSTRACT

Different types of mycoses, especially invasive mycoses caused by yeasts and molds, are a growing problem in healthcare. *Candida albicans* is one of the most common opportunistic fungi responsible for these kinds of infections. The most notable explanation for this increase is a rise in the number of immunocompromised patients owing to advances in transplantation, the emergence of AIDS and a rise in the number of invasive surgical procedures. Conveniently accessible hydrazide derivatives of benzoic acid 1 were converted to new thiosemicarbazides, triazoles and alkylthiotriazoles. The antibacterial and antifungal activities were determined. Some of the newly synthesized compounds showed weak corresponding activities.

INTRODUCTION

Triazoles are associated with diverse pharmacological activities such as anti-bacterial[1], antifungal[2], anti-inflammatory[3], anticonvulsant[4], antimalarial[5], antiviral[6], antileuneer[7], anti-TB[8], and anti-proliferative activities[9]. Similar activities are also reported for the acylthiosemicarbazides[10-17].

Triazoles, as an important type of fungicides, display this effect through interference with sterol synthesis.[18] They displace lanosterol from its site in cytochrome p-450 C14 α demethylase preventing its conversion to ergosterol. Ergosterol is an essential component of the fungal cell membranes and hence in its function and permeability.[19] The net result is an inhibition of fungal growth and eventually the death of the microbe. A number of the prepared compounds are tested against several pathogenic fungi and the results revealed that some of the new compounds showed some activity while others are not.

CHEMISTRY

The synthesis of the compounds was initiated through p-nitrobenzoic acid which is prepared starting from p-nitrotoluene using the method adopted in Vogel by oxidation with sodium dichromate and sulfuric acid. Conversion the acid to its methyl ester is done by heating with methanol with a catalytic amount of sulfuric acid. The acid hydrazide is formed through a reaction with excess hydrazine hydate (3-4 folds) in alcohol to give the nearly pure acid hydrazide which is further reacted with the appropriate isothiocyante in alcohol to give N1-substituted-4-acylthiosemicarbazides. The later compounds then cyclized to the corresponding triazoles 1 using aqueous 2N sodium hydroxide[20]. The method of alkylation used involves stirring of the triazole and potassium hydroxide in alcohol till a clear solution is attained then the appropriate alky halide is added with stirring and heating is continued for 8 hours to give 2a-f.

The benzamidobenzoyl thiosemicarbazides 4a-f are prepared starting from benzocaine, which is acylated with benzoyl chloride in pyridine, the ethyl benzamidobenzoate then reacted with several folds (4-6) of hydrazine in the minimal amount of alcohol to give benzamidobenzoylhydrazine[21] 3. Compounds 4a-f are prepared by either heating with Isothiocyanates in alcohol or using the method of Baxter et al[22] which involves prior preparation of the isothiocyanate (only the aryl isothiocyanates in situe from the corresponding aryl thiourea by heating in chlorobenzene for at least 6-8 hours then removal of the organic solvent under a mild heat and a high vacuum).

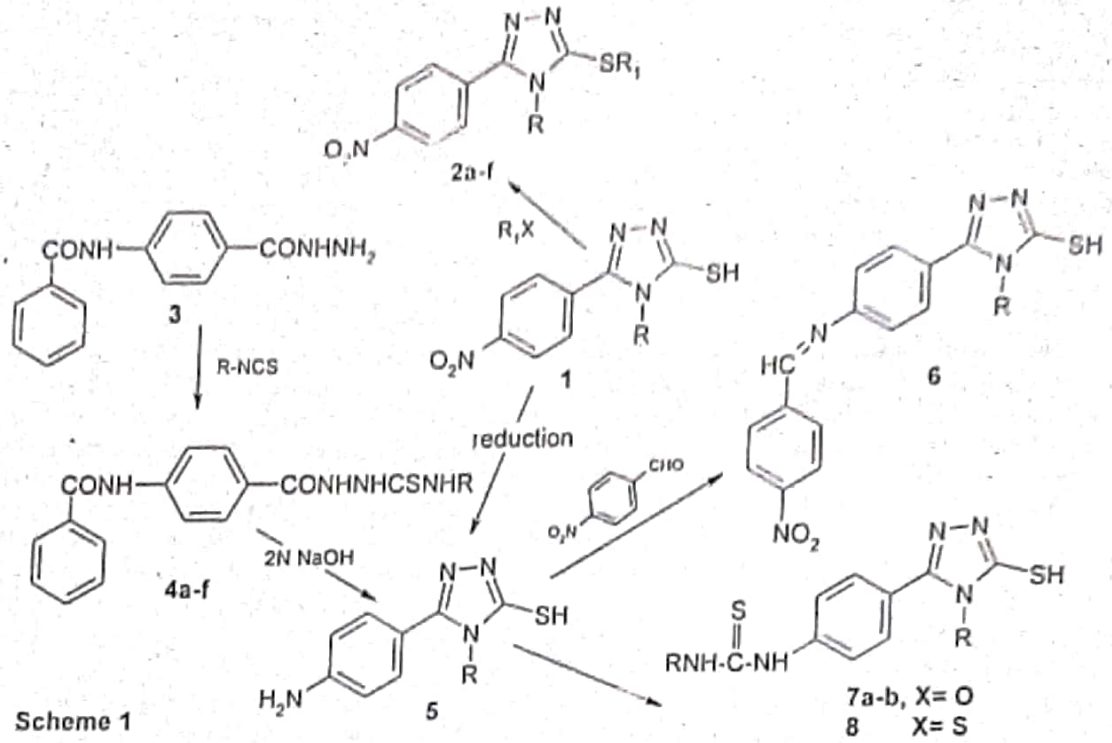
Compound 5 is prepared by hydrolysis of 4a in 10% sodium hydroxide followed by neutralization with hydrochloric acid[23]. The later is reacted with 4-nitrobenzaldehyde in absolute ethanol to give 6. Reaction of 5 with the appropriate isocyanates gave 7a-b. Benzoyl isothiocyanate, prepared by mixing equal amounts of benzoyl chloride and ammonium thiocyanate in acetone, is reacted with 5 by heating for few minutes followed by hydrolysis with aqueous sodium hydroxide to give compound 8. (Scheme 1) .Compound 11 was prepared by stirring benzocaine 9 on cold with cyclohexylisocyanate in acetone then the nearly pure ester 10 is reacted with hydrazine hydrate in alcohol to afford 11 which upon reaction with ethyl isothiocyanates gave 12. (Scheme 2)

EXPERIMENTAL

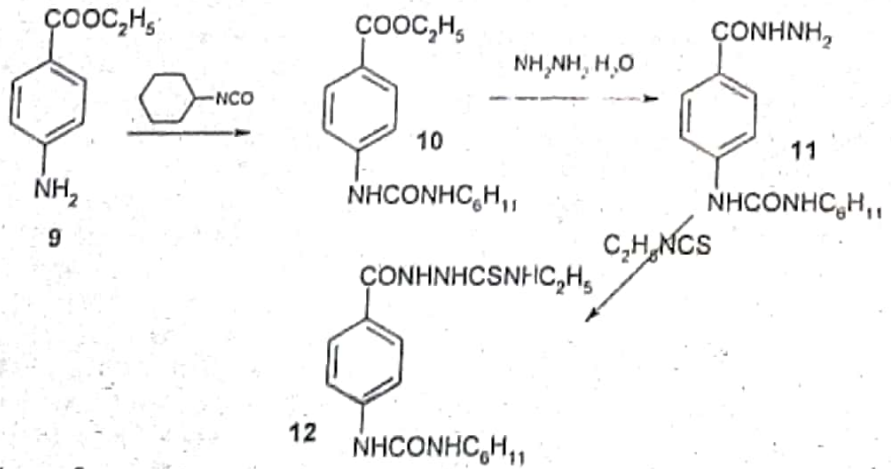
Melting points were determined on Gallenkamp melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed by Micro Analytical Center, Faculty of Science, Cairo University. Infrared spectra were recorded on Shimadzu IR FTR Spectrophotometer using KBr discs. ^{1}H NMR spectra were scanned on Varian mercury 300 MHz (chemical shifts are given in part per million (ppm) downfield from TMS). Mass spectrometric analysis (HPLC-ESI-MS) was performed on a TSQ quantum (Thermo Electron Corporation) instrument equipped with an ESI source and a triple quadrupole mass detector pole (Thermo Finngan, San Jose CA.)

4-Substituted-5-alkylthio-2-nitrophenyl-1,2,4-triazole 2a-f:

The triazole derivatives 1 (10 mmol) were added to potassium hydroxide (0.56 gm 10 mmol) in ethanol (20 mL) and stirred on cold. The solution obtained was filtered and the appropriate alkyl halide (10 mmol) was added and the mixture is heated for 8 hours, filtered concentrated then water was added and the separated solid was collected by filtration and crystallized from the appropriate solvent. Compounds **2a-f** (Table 1)



Scheme 1



Scheme 2

4-Benzamidobenzoylthiosemicarbazides 4a-f:

Method A:

To a solution of **3** (2.55 gm, 10 mmol.) in ethanol (20 mL), the appropriate isothiocynate (10 mmol.) was added. The mixture was refluxed for 8 hours, cooled and the separated solid was filtered, dried and crystallized from the appropriate solvent. Compounds **4a-f.** (Table 2)

To a solution of **3** (2.55 gm, 10 mmol.) in ethanol (20 mL), the appropriate isothiocynate (10 mmol.) was added. The mixture was refluxed for 8 hours, cooled and the separated solid was filtered, dried and crystallized from the appropriate solvent Compound. 4a-f Table 2

Method B:

A mixture of the aryl thiourea (10 mmol) and chlorobenzene (20 mL, was heated carefully under reflux for 6-7 hours, most of the organic solvent is evaporate in vacuum and the residue was dissolved in ethanol (20 mL) followed by the acid hydrazide (2.55gm, 10 mmol) and refluxing is continued for 7 hours. The separated solid is collected by filtration, washed with dilute alcohol then crystallized from the appropriate solvent. (Table 2)

2-p-Aminophenyl-5-mercapto-1,2,4-triazole 5:

Compound 3a (5 gm) was heated with 10 % NaOH (50 mL) for 2 hours, the obtained solution obtained was diluted with water filtered and the filtrate is neutralized with dilute HCl. The separated is filtered then crystallized from alcohol to give compound 5 m.p. 250 ^{0}C.

IR spectrum of 5 revealed (cm^{-1}): 3466, 3356 (NH_2), 1620 (C=N).

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4-Ethyl-3-(4- nitrobenzylidene-amino)-5-mercapto-1,2,4-triazole 6:

A mixture of 5 (2.2gm.10 mmol) p-nitrobenzaldehyde (1.51gm 10 mmol), few drops acetic acid in alcohol (25 ml.) was heated under reflux and stirring was continued for 10 hours and the separated solid filtered and crystallized from DMF- H_2O to give 6 yield % 65 m.p. 288-9 °C.

Analysis for $C_{11}H_{15}N_5O_2S$ calc. C 57.79 H 4.24 N 19.83. Found C 57.85 H 3.99 N 19.60.

2-Substituted ureido-4-ethyl-5-mercapto-triazoles 7a-b:

A mixture of 5 (1.1gm 5 mmol) ,the appropriate isocynate (5 mmol) and acetone (15 mL) was heated under reflux and stirring for 4 hours and the separated solid filtered and reerystalized **7a-b (Table 3)**

4-Ethyl-5-mercapto-3-thioureidophenyl triazole 8:

Benzoylisothiocyanate (11 mmol), made in situe by mixing equlmolar amounts of benzoyl chloride and ammonium isothiocyanate in acetone, was added with continuous stirring to 5 (2.2gm, 10 mmol) in acetone .The obtained solution is refluxed for further 30 minutes and 2N NaOH (40 mls) is added and the mixture is heated for 2 hours then filtered. HCl is added to the filtrate and the solid 8 separated is crystallized from ethanol. Yield 77% m.p.240 °C.

Analysis for $C_{11}H_{13}N_5S_2$ calc. C 47.31 H 4.6 N 25.08 found C 47.06 H 4.77 N 25.31

4-Cyclohexylureidobenzhydrazide 11:

Cyclohexyl isocyanate (1.25gm 10 mmol) is added to benzocaine 9 (1.65gm 10 mmol) dissolved in acetone (20mL) and stirred on cold overnight concentrated and the separated product is collected washed with ether filtered. The separated solid then is dissolved in alcohol, hydrazine hydrate (4 ml) is added and the mixture is refluxed for 4 hours. The separated solid is collected by filtration and crystallized from ethanol to give compound 9 Yield 75% m.p 245-6 °C. Analysis for $C_{14}H_{20}N_4O_2$ calc. C 60.86 H 7.24 N 20.28 found C 60.63 H 7.4 7N 20.19. H NMR (D MSO, 300 MHz) δ(ppm): 1.22 (m, 4H, 3.5 CH_2- of C_6H_{11} -). 1.68 (m, 2H 4-CH_2- of C_6H_{11} -) 1.76 (m, 4H, 2,6-$CH_2$of C_6H_{11} -) 3.5 (m, 1H, 1-CH- of C_6H_{11} -) 4.4 (-NH_2) 6.16,8.51,9.50 (NHs.), 7.41(d, 2H, 2,6 ArH), 7.71 (d, 2H, 3.5 ArH)

4-Cyclohexylureidobenzoyl-1-ethyl-thiosemicarbazide 12:

A mixture of and ethyl isothiocyanate in alcohol is refluxed for 5 hours, concentrated and the residue is crystallized from DMF-H_2O to give **12**. Yield 80% m.p. 220 °C

Analysis for $C_{17}H_{25}N_5O_2S$ calc. C 56.19 H 6.88 N 19.28 found C 55.99 H 6.71 N 19.11.

12,IR (cm^{-1}): 3352, 3309 (NH,NH_2), 1658(C=O), 1589 (C=C), m/z, M+1 = 364

ANTIMICROBIAL ACTIVITY

Methods:

The antimicrobial activity of 8 compounds (**1a,2b,2f,3,4a,4b,7b** and **12**) were tested against representatives of acid fast bacilli (*Mycobacterium phlei*), Gram-positive bacteria (*Bacillus subtilis, Staphylococcus aureus and Sarcina lutea*), Gram-negative bacteria (*Escherichia coli, Proteus vulgaris and Pseudomonas aeruginosa*) and some representative fungal species yeast (*Candida albicans*), mycelial fungi (*Aspergilusu niger, Aspergillus fumigatus, Aspergillus flavus and Penicillium vermiculatum*). Applying the disc agar diffusion method[24,25] using trypticase soy agar for bacteria and yeast and MIC in solid medium for mycelial fungi as well as tested bacterial strains. The products were dissolved in DMSO at concentration of 10 mg/ml then 20 µl were aseptically transferred onto sterile discs (200 µg/disc) of Whatman filter paper (5 mm diameter). The charged discs were ascetically transferred onto the surface of dried inoculated Tryticase soy agar plates.

The discs were then placed onto the surface of the inoculated plates previously prepared. The plates were incubated inverted at 37 °C for 24 hr in case of bacteria and at 25 °C for 48 hr in case of fungi (yeasts). After incubation, the inhibition zones were recorded in mm. Diameter less than 5 mm indicates no effect. A disc impregnated with 20 µl of DMSO is used as a negative control as well as discs of Ofloexacine (OFX) and Amphotricin B, (AMP B), 5µg/disc each were used as a positive control).

The MIC was determined for bacteria and fungal species were tested against 200,100, 50, 25 and 12.5 (µg/ml) concentrations of the tested compounds in DMSO incorporated in agar. Then 20µl of each dilution was transferred in cups preformed in Trypticase soy agar inoculated with suspension of 10^5/ml yeast cells or fungal spores

the surface of agar plates and incubated at 30°C for 4-5 days. After incubation the lowest concentration producing inhibition was recorded as the minimum effective concentration.

RESULTS AND DICUSSION

All the tested products revealed either no antimicrobial effect or very weak activity against both of Gram-positive & Gram negative bacteria as well as fungi. Also, some effect was observed with compounds (2f, 12) against Gram-positive, Gram-negative with MIC level between 25- 50 µg /ml for bacterial strains and between 12.5 – 100 µg /ml for fungal species (Table 4, 5, 6). Compound (**4b**) showed week activity against some Gram-negative bacteria with MIC level 50 µg /ml, On the other hand Compounds (**1, 3, 7b**) showed week activity against some Gram-positive bacteria with MIC level between 25- 100 µg /ml.

The bacterial strains were highly resistant to products 1, 2b,3, 4b, 7b, 12 MIC level > 200 µg /ml. In addition, no

or antimycobacterial activity was detected with the tested products with MIC level 100- > 200 µg /ml. With respect to Fungal species, only compounds (2f, 4a) having some activity with MIC level ranged between 12.5- 200 µg /ml. On the other hand all the fungal strains were highly resistance to compounds (1, 2b,3, 4b, 7b, 12) MIC level 200 µg /ml

Table (1) Chemical and physical data of compounds 2a-f

Comp No.	R	R_1	m.p °C	Yield% Crystal. solvent	Molecular formula (M. Wt.)	Microanalysis	Calc.%	Found%
2a	C_2H_5	CH_3	164-5	75 alcohol-water	$C_{11}H_{12}N_4O_2S$ 264	C H N	49.99 4.54 21.21	50.30 4.83 21.52
-b	C_2H_5	C_2H_5	142-4	80 alcohol	$C_{12}H_{14}N_4O_2S$ 278	C H N	51.79 5.03 20.14	51.96 4.88 20.02
-c	C_2H_5	C_3H_7	138-9	88 alcohol	$C_{13}H_{16}N_4O_2S$ 292	C H N	53.42 5.47 19.17	53.21 5.77 18.93
-d	C_2H_5	C_4H_9	160-1	72 alcohol	$C_{14}H_{18}N_4O_2S$ 306	C H N	54.90 5.88 18.3	54.59 5.80 18.00
-e	C_4H_9	C_3H_7	106-7	70 alcohol	$C_{15}H_{20}N_4O_2S$ 320	C H N	56.25 6.25 17.50	55.98 5.88 17.22
-f	C_4H_9	C_7H_7	148-9	85 alcohol	$C_{19}H_{20}N_4O_2S$ 368	C H N	61.95 5.43 15.21	61.95 5.11 15.00

1b, IR (cm^{-1}): 3082 (CH aromatic), 2959, 2927, 2870 (H aliphatic) 1600 (C=C).
2a, m/z , M+1 = 265.
2b, IR (cm^{-1}): 3089 (CH aromatic), 2978, 2931, 2870 (H aliphatic) 1601 (C=C). **m/z ,** M+1 =279.
2c: IR (cm^{-1}): 3089 (CH aromatic), 2970, 2927, 2866 (H aliphatic) 1600 (C=C). **m/z ,** M+1 =293.
2d, IR (cm^{-1}): 3078 (CH aromatic), 2966, 2935, 2870 (H aliphatic) 1600 (C=C).
2e IR (cm^{-1}): 3082(CH aromatic), 2962, 2931, 2870 (H aliphatic) 1600 (C=C).
m/z , M+1 =321. H-NMR (DMSO-d$_6$, 300 MHz) δ(ppm): 78 (t, 3H, - $CH_3\underline{CH_2}CH_2CH_2CH_2CH_2CH_3$), 1.07 (m, 2H, $CH_3\underline{CH_2}CH_2CH_2CH_2CH_2$),1.39 (d, 6h 2-$CH_3$ isopropyl), 1.48 (2 H $CH_3CH_2\underline{CH_2}CH_2$-), 3.81 (m, 1H, isopropyl H), 4.06 (m, 2H, $CH_3CH_2CH_2\underline{CH_2}$-),8.01 (d, 2H, 2,6 ArH), 8.4 (d, 2H, 3.5 ArH).
2f: m/z , M+1 =369

Table (2) Chemical and physical data of compounds 4a-f

Comp No.	R	m.p°C	Yield% Crystal. solvent	Molecular formula (M. Wt.)	Microanalysis	Calc %	Found%
4a	C_2H_5	220-2	85 alcohol	$C_{17}H_{18}N_4O_2S$ 342	C H N	59.64 5.26 16.37	59.64 5.34 16.15
-b	C_3H_5	223-5	69 alcohol	$C_{18}H_{18}N_4O_2S$ 354	C H N	61.01 5.08 15.81	60.05 5.12 15.57
-c	C_4H_9	220-1	76 alcohol	$C_{19}H_{22}N_4O_2S$ 370	C H N	61.62 5.94 15.13	61.38 5.91 15.43
-d	C_6H_5	280-2	65 DMF-H_2O	$C_{21}H_{18}N_4O_2S$ 390	C H N	64.61 4.61 14.35	64.53 4.16 14.62
-e	C_6H_{11}	218-20	73 alcohol	$C_{21}H_{24}N_4O_2S$ 396	C H N	63.63 6.06 14.14	63.88 5.84 13.68
-f	p-$CH_3OC_6H_4$-	226-8	65 alcohol	$C_{22}H_{20}N_4O_2S$ 420	C H N	62.85 4.76 13.33	62.44 4.40 12.98

3, IR (cm^{-1}): (cm^{-1}): 3329, 3282 (NHs, NH_2); 3000 (CH aromatic), 1705, 1658 (C=O,), 1608 (C=C).
4a , IR (cm^{-1}): (cm^{-1}): 3313, 3267, 3244 (NHs), 2970 (CH aromatic), 1670, 1654 (C=O,), 1593(C=C).

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4b , IR (cm^{-1}): (cm^{-1}): 3245, 3232, (NHs), 1670, 1651 (C=O), 1600 (C=C), m/z , M+1 -355. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.37 (m, 2H, -CH_2 CH CH_2), 5.11 (2 H, -CH_2 CH CH_2) 5.8(m, 1H, -CH_2 CH=CH_2) 4.08, 8.2, 9.30, 10.25 (NHs,), 7.59(d, 2H, 2,6, ArH), 7.95 (d, 2H, 3,5 ArH).
4e, IR (cm^{-1}): (cm^{-1}): 3317, 3275, 3201 (NHs), 2954 (CH aliphatic), 1666, 1651 (C=O), 1567(C=C), 4e: m/z, M^+ =397.
4f, IR (cm^{-1}): (cm^{-1}): 3250, 3209 (NHs), 3020(CH aromatic) ,1608 (C=O), m/z, M+1- 421. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.74 (s, 3H, CH3O), 6.90 (m, 2H, phenoxy)7.3 ((m, 2H, phenoxy) 7.62 (m, 4H, H- aryl) 90 (m,5H, H-aryl) 9.54,10.4, 10.57(NHs).

Table(3) Chemical and physical data of compounds 7a-b

Comp No.	R	m.p°C	Yield% Crystal. solvent	Molecular formula (M. Wt.)	Microanalysis		
					Calc.%		Found%
7-a	C_6H_{11}	210-2	85 DMF-H_2O	$C_{17}H_{18}N_4O_2S$ 342	C H N	59.13 6.66 20.28	59.4 7.00 20.80
7-b	C_6H_5	246-8	69 DMF-H_2O	$C_{18}H_{18}N_4O_2S$ 354	C H N	60.17 5.01 20.64	60.28 4.94 20.33

Table (4): Antimicrobial activity of the tested compounds.Diameter of inhibition zone in mm

Microorganisms	1	2b	2f	3	4a	4b	7b	12	OFX*	AMP.B*
Proteus vulgaris NCTC 4175	-	-	-	-	-	-	-	-	25	-
Bacillus subtilis NCTC 6633	-	-	-	-	-	-	10	8	29	-
E.coli ATCC 10536	-	-	6	-	-	-	-	-	28	-
*Sarcina lutea**	-	-	7	-	-	-	7	-	28	-
Pseudomonas aeruginosa CNCM A21	-	-	8	-	-	7	-	9	25	-
Staphylococcus aureus ATCC 4175	8	-	8	8	-	-	9	-	31	-
*Mycobacterium phlei**	-	-	-	-	-	-	-	-	27	-
*Candida albicans**	-	-	9	-	-	-	-	-	-	21

OFX: Ofloxacin (5 µg/disc) AMP. B: Amphotricin B (5 µg/disc) positive control.

Table (5): Antimicrobial activity of the tested compounds (MIC µg/ml).

Microorganisms	1	2b	2f	3	4a	4b	7b	12	OFX
Proteus vulgaris NCTC 4175	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	1
E.coli ATCC 10536	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	3
Pseudomonas aeruginosa CNCM A21	50	> 200	50	> 200	> 200	50	> 200	25	2
Bacillus subtilis NCTC 6633	> 200	> 200	> 200	> 200	> 200	> 200	25	> 200	0.5
Staphylococcus aureus ATCC 4175	50	> 200	50	50	> 200	> 200	50	> 200	2
Sarcina lutea	50	> 200	50	50	> 200	> 200	100	> 200	2
*Mycobacterium phlei**	> 200	> 200	> 200	> 200	> 200	> 200	> 200	> 200	2

Table (6): Antimicrobial activity of the tested compounds against fungal species (MIC µg/ml).

Microorganisms	1	2b	2f	3	4a	4b	7b	12	AMP B
*Candida albicans**	> 200	> 200	50	> 200	> 200	> 200	> 200	> 200	2
Aspergilus niger	200	200	25	200	25	200	200	200	0.5
Aspergillus fumigatus	> 200	200	50	200	100	200	200	200	1
Aspergillus flavus	> 200	200	50	200	100	200	200	200	1
Penicillium vermiculatum	> 200	> 200	50	200	200	200	200	200	2

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تشييد واختبار الفاعلية الميكروبيولوجية لبعض الترايازولات وحامض البارا أمينوبنزويك

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