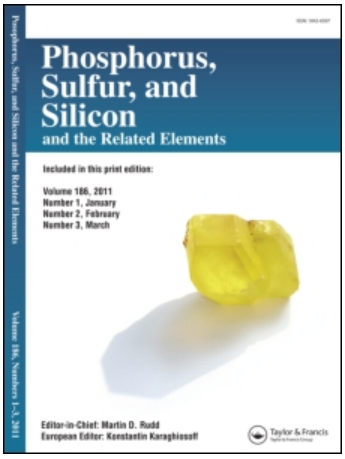

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SYNTHESIS OF SOME NEW 3-MERCAPTO-5-SUBSTITUTED-1,2,4-TRIAZINE-S-TRIAZOLES FOR EVALUATION AS ANTIBACTERIAL AGENTS

Zakaria K. Abd El-Samii[a]; Said A. El-feky[a]
[a] Pharmaceutical Chemistry Department, Faculty of Pharmacy, Al-Fateh University, Tripoli, Libya

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SYNTHESIS OF SOME NEW 3-MERCAPTO-5-SUBSTITUTED-1,2,4-TRIAZINE-S-TRIAZOLES FOR EVALUATION AS ANTIBACTERIAL AGENTS

ZAKARIA K. ABD EL-SAMII and SAID A. EL-FEKY
Pharmaceutical Chemistry Department, Faculty of Pharmacy, Al-Fateh University, Tripoli, Libya

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The synthesis of several S- and N-substituted derivatives of 5-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole-3-thiol, 2-[(5-6-diphenyl-1,2,4-triazin-3-yl)-oxymethyl]-5,6-dihydrothiazolo[3,2-b]-s-triazole, 2-[(5,6-diphenyl-1,2,4-triazin-3-yl) oxymethyl]-6,7-dihydro-s-triazolo-[5,1-b]-1,3-thiazine, 2-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-5,6-dihydrothiazolo-[3,2-b]-s-triazol-6-one and 2-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-6-phenylthiazolo-[3,2-b]-s-triazole is reported. All the novel compounds have been screened for antibacterial activity and none of them showed noteworthy activity.

Key words: 1,2,4-triazines, s-triazoles, thiazolo-[3,2-b]-s-triazoles, s-triazolo-[5,1-b]-1,3-thiazine.

INTRODUCTION

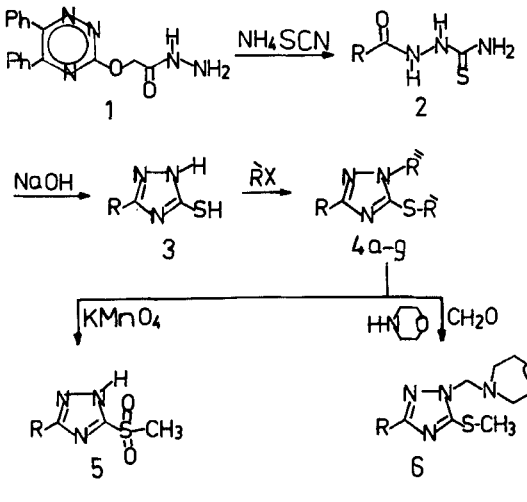
Recent investigation has demonstrated significant biological activity of 5,6-diphenyl-1,2,4-triazine nucleus.[1-3] Of more particular interest are the diverse pharmacological activities displayed by a variety of 1,2,4-triazine containing s-triazoles.[1,2] In addition to in vitro antibacterial activity,[4] certain thiazolo-[3,2-b]-s-triazoles have shown antiinflammatory and analgesic antipyretic activity.[5]

In an effort to capitalize on the biological potential of these heterocyclic systems and in continuation of our program on the synthesis of biologically active 1,2,4-triazines,[1,2,6] we undertook the synthesis of the compounds herein described.

RESULTS AND DISCUSSION

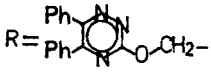
The sequence of reactions followed in the synthesis of the target compounds is illustrated in the following schemes.

Cyclization of 1-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxyacetyl]-3-thiosemicarbazide[6] (**2**) by refluxing with aqueous sodium hydroxide following the reported procedure[7] yields the pertinent 5-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole-3-thiol (**3**). The thiol 3 was in turn reacted with methyl or ethyl iodide and substituted benzyl halides in N,N-dimethylformamide containing potassium hydroxide adopting the procedure of Draper and Castle[8] to give the expected S-substituted derivatives (**4a–d**). The IR spectra of compounds **4a–d** showed characteristic absorption bands at 3390–3350 (NH). S-alkylation was also confirmed by oxidation of **4a** using potassium permanganate,[9] where a methylsulfonyl derivative (**5**) was obtained in which a downfield shift was observed in the methyl protons in ^{1}H NMR. On the other hand, refluxing **3** for 12 hr. with three equivalents of methyl or benzyl halides

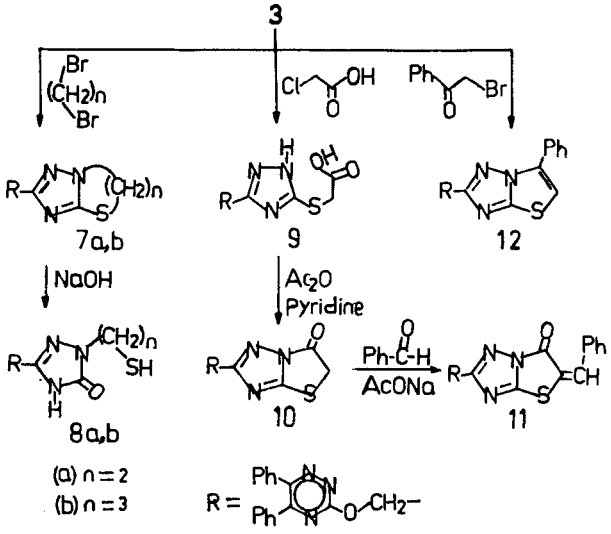


Compd.	4a	4b	4c	4d
R'	CH_3	C_2H_5	$CH_2C_6H_5$	$CH_2C_6H_4(4\text{-}Cl)$
R''	H	H	H	H

Compd.	4e	4f	4g
R'	CH_3	C_2H_5	$CH_2C_6H_5$
R''	CH_3	C_2H_5	$CH_2C_6H_5$

R = 

SCHEME I



SCHEME II

in acetone and in the presence of potassium carbonate[9] afforded S- and N-substituted 4-triazoles (**4e–g**). The IR spectra of compounds **4e–g** showed the disappearance of the characteristic NH bands. Furthermore, the structures of **4e–g** were confirmed by an alternative synthesis. Reaction of **4a–c** with one mole of methyl

or benzyl halides in acetone and in the presence of potassium carbonate produced the aforementioned S- and N-substituted derivatives.

3-Methylthio-5-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole **4a** was subjected to aminomethylation[7] using Mannich reaction conditions in the presence of morpholine to afford 2-morpholinomethyl-3-methylthio-5-(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole.[6]

The reaction of 3 with 1,2-dibromoethane[10] resulted in the formation of 2-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-5,6-dihydrothiazolo-[3,2-b]-s-triazole (**7a**). The IR spectrum of this product showed the absence of NH and SH absorption frequencies indicating cyclization. A similar reaction of **3** with 1,3-dibromopropane furnished 2-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-6,7-dihydro-s-triazolo-[5,1-b][1,3]-thiazine (**7b**). Compounds **7a** & **b** were refluxed with sodium hydroxide[10] solution to give 2-(2-mercaptoethyl)-5-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-3(4H)-s-triazolone (**8a**) and 2-(3-mercaptopropyl)-5-[5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-3(4H)-s-triazolone (**8b**), respectively.

The thiol **3** was reacted with chloroacetic acid[5] in the presence of sodium hydroxide to provide the corresponding 3-carboxymethylthio-5-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole (**9**). Compound **9** was in turn reacted with acetic anhydride and pyridine[5] to give 2-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-thiazolo-[3,2-b]-s-triazol-6-one (**10**). Reaction of **10** with benzaldehyde in the presence of sodium acetate yielded the 5-benzylidene derivative (**11**).

Compound **3** on condensation with phenacyl bromide in the presence of sodium acetate[11] yielded 2-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-6-phenylthiazolo-[3,2-b]-s-triazole (**12**).

All the new compounds (**3–12**) were tested for their antibacterial and antifungal activity against Staphylococcus aureus, Escherichia coli and Candida albicans by measuring the inhibition zone produced by each compound using the agar plate diffusion method.[12] However, none of the compounds reported herein showed any noteworthy activity.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded using KBr discs (ν_{max} in cm^{-1}) on a Pye Unicam Sp-1000 spectrophotometer. ^1H NMR spectra were obtained on a Varian T60 spectrometer using DMSO-d_6 as the solvent and TMS as an internal reference (Chemical shift in δ ppm). Elemental analyses were carried out at University College, London.

The intermediate 1-(5,6-diphenyl-1,2,4-triazin-3-yl)oxyacetyl-3-thiosemicarbazide (**2**) was prepared according to our reported procedure[6] from (5,6-diphenyl-1,2,4-triazin-3-yl)oxyacetylhydrazide (**1**).[5]

5-[(5,6-Diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole-3-thiol (**3**): A mixture of 1-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxyacetyl]-3-thiosemicarbazide (**2**) (0.01 mole) in 8% sodium hydroxide (100 ml) was refluxed for 5 hours. The reaction mixture was cooled and acidified with dilute acetic acid. The precipitate thus obtained was filtered, washed with water and crystallized from ethanol. This afforded (**3**) in 60% yield, m.p. 250–252°; IR: 1590 (C=N), 3310 (NH), 2900 (SH).

^1H NMR: 3.8 (s, 2H, OCH_2), 6.9–7.3 (m, 10H, Ar—H).
Analysis: $C_{18}H_{14}N_6OS$ (362.405)
Calculated C, 59.65, H, 3.89; N, 23.18
Found C, 60.0; H, 3.7; N, 23.5

3-(Alkylthio)-5[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazoles (**4a–d**): Compound **3** (0.30 mole) was dissolved in N,N-dimethylformamide (DMF) (25 ml) to which potassium t-butoxide (0.35 mole)

had been added. When **3** was completely dissolved, the appropriate alkyl halide (0.32 mole) was added and the mixture was stirred at about 50° for six hours. The mixture was then poured into 200 ml of water, and the resulting flocculent tan precipitate was cooled and washed well with water. The analytical samples were prepared by recrystallization from ethanol to give **4a–d** (Table I).

4a: ^{1}H NMR (DMSO-d_6): 2.85 (s, 3H, SCH_3), 3.95 (s, 2H, OCH_2), 7–7.5 (m, 10H, Ar—H).

2 (Alkyl)-3-Alkylthio-5[5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazoles (**4d–g**).

Method a: Compound **3** (0.005 mole) was dissolved in acetone (30 ml) to which anhydrous potassium carbonate (0.02 mole) had been added. The appropriate alkyl halide (0.015 mole) was added and the mixture was stirred at about 50° for twelve hours. The mixture was cooled, treated with water (100 ml) and left overnight in the refrigerator. The separated precipitate was filtered, and washed well with water. Recrystallization from ethanol gave **4d–g** (Table I).

Method b: The same as method a, but reacting **4a–d** with the appropriate alkyl halide (equimolar amounts).

TABLE I

Physical data of 2-(alkyl), 3-(alkylthio)-5[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazoles (**4a–g**)

Compd. No.	R′	R″	Yield (%)	M.P (°C)	Formula (Mol. Wt.)	Analys s % Calcd./Found		
						C	H	N
4a	CH_3	H	95	165–167	$C_{19}H_{16}N_6OS$	60.63	4.28	22.32
					(376.37)	60.3	4.3	22.0
4b	C_2H_5	H	90	202–204	$C_{20}H_{18}N_6OS$	61.52	4.64	21.52
					(390.459)	61.6	4.5	21.6
4c	$CH_2C_6H_5$	H	80	155–157	$C_{25}H_{20}N_6OS$	66.35	4.45	18.57
					(452.53)	66.2	4.5	18.5
4d	$CH_2C_6H_4$- (4 Cl)	H	75	208–210	$C_{25}H_{19}ClN_6OS$ (487.022)	61.66 61.5	3.93 4.0	17.25 17.0
4e	CH_3	CH_3	55	180–182	$C_{20}H_{18}N_6OS$	61.52	4.64	21.52
					(390.459)	61.8	4.8	21.8
4f	C_2H_5	C_2H_5	65	142–144	$C_{22}H_{22}N_6OS$	63.13	5.29	20.07
					(418.513)	63.0	5.0	20.0
4g	$CH_2C_6H_5$	$CH_2C_6H_5$	70	135–137	$C_{32}H_{26}N_6OS$	70.82	4.82	15.48
					(542.655)	70.7	5.0	15.6

TABLE I (*Continued*)

Compd. No.	IR (cm^{-1})	^{1}HNMR (DMSO-d_6)
4a	3370	2.85 (s, 3H, SCH_3), 3.95(s, 2H, OCH_2), 7 - 7.5 (m, 10H, Ar H)
4b	3350	1.5 (t, 3H, CH_3), 3.2 (q, 2H, CH_2), 4.0 (s,2H,OCH_2), 7.1-7.55 (m, 10H, Ar-H)
4c	3385	3.96 (s, 2H, OCH_2), 4.5 (s, 2H, CH_2), 7.0 - 7.5 (m, 15H, Ar-H).
4d	3390	4.1 (s, 2H, OCH_2), 4.55 (s, 2H, CH_2), 7.0-7.7 (m, 14H, Ar-H).
4e	-	2.73 (s, 3H, SCH_3), 3.76 (s, 3H, N-CH_3), 4.0 (s, 2H, OCH_2), 7.1-7.5 (m,10H, Ar-H)
4f	-	1.13 (t, 3H, CH_3), 1.56 (t, 3H, CH_3), 3.2 (q, 2H, CH_2), 4.06 (q, 2H, CH_2), 4.2 (s, 2H, OCH_2), 7.1-7.5 (m, 10H,Ar-H)
4g	-	4.0 (s, 2H, OCH_2), 4.4 (s, 2H, SCH_2), 4.66 (s,2H, NCH_2), 7.0-7.8 (m,20H, Ar-H)

3-(Methylsulphonyl)-5-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole (**5**). Compound **4a** (2.5 g) in acetic acid (30 ml) was added while stirring to a solution of potassium permanganate (1.5 g) in water (10 ml). Stirring was continued for 30 minutes, then the mixture was decolorized with sodium bisulphite and filtered. The resulting solid was washed well with water and crystallized from ethanol to give **5** in 60% yield, m.p. 220–222°.

IR: 3350 (NH), 1360 and 1150 $(SO)_2$; ^{1}H NMR: 3.7 (s, 3H, SO_2CH_3), 4.0 (s, 2H, OCH_2), 7.1–7.5 (m, 10H, Ar—H).

Analysis: $C_{19}H_{16}N_6O_3S$ (408.42)
Calculated: C, 55.87; H, 395; N, 20.60
Found: C, 55.5; H, 3.8 N, 20.5

2-Morpholinomethyl-3-methylthio-5-[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole (**6**). An ethanolic solution of **3a** (0.05 mole) was stirred with 37% formaldehyde solution (1 ml) and an ethanolic solution of morpholine (0.09 mole) for two hours at room temperature. The reaction mixture was kept in a refrigerator overnight and the precipitate was filtered, washed with cold ethanol and recrystallized from absolute ethanol to give **6** in 80% yield; m.p. 170–172°. ^{1}H NMR: 2.63 (s, 3H, SCH_3), 2.8 (m, 4H), 3.76 (m, 4H), 4.5 (s, 2H, OCH_2), 5.26 (s, 2H, CH_2), 7–7.5 (m, 10H, Ar—H).

Analysis: $C_{24}H_{25}N_7O_2S$ (475.55)
Calculated: C, 60.61; H, 5.30; N, 20.6
Found: C, 60.5; H, 5.3; N, 20.5

2-[(5,6-Diphenyl-1,2,4-triazin-3-yl)-oxymethyl]-5,6-dihydrothiazolo-[3,2-b]-s-triazole (**7a**), *2-[(5,6-Diphenyl-1,2,4-triazin-3-yl)-oxymethyl]-6,7-dihydro-s-triazolo[5,1-b][1,3]-thiazine* (**7b**). Compound **3** (0.35 mole) was added slowly to a stirred mixture of DMF (15 ml), 1,2-dibromoethane or 1,3-dibromopropane (0.40 mole) and anhydrous sodium carbonate (4.5 g). After two hours at room temperature, the reaction mixture was heated with stirring for 10–12 hours at 60–65° and then refrigerated overnight. The mixture was then poured into water (200 ml) and the resulting precipitate was collected and washed well with water. Recrystallization from ethyl alcohol gave **7a** and **7b**.

7a: was obtained in 40% yield; m.p. 270–273; ^{1}H NMR: 3.41 (t, 2H, SCH_2), 4.17 (t, 2H, NCH_2), 4.5 (s, 2H, OCH_2), 7.1–7.5 (m, 10H, Ar—H).

Analysis: $C_{20}H_{16}N_6OS$ (388.443)
Calculated: C, 61.84; H, 415; N, 21.63
Found: C, 61.6; H, 4.0; N, 21.8

7b: was obtained in 30% yield, m.p. 250–252°. ^{1}H NMR: 2.0 (m, 2H, CCH_2C), 3.12 (t, 2H, SCH_2), 3.80 (t, 2H, NCH_2), 4.53 (s, 2H, OCH_2), 7.1–7.5 (m, 10H, Ar—H).

Analysis: $C_{21}H_{18}N_6OS$ (402.47)
Calculated: C, 62.67; H, 4.50; N, 20.88
Found: C, 62.6; H, 4.3; N, 20.9

2-(2-Mercaptoethyl)-5[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-3(4H)-s-triazolone (**8a**), *2-(3-Mercaptopropyl)-5[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-3(4H)-s-triazolone* (**8b**). A suspension of **7a** or **7b** (0.03 mole) in 2 N sodium hydroxide solution was refluxed for four hours. The resultant solution was acidified with hydrochloric acid (1:1 V:V) to pH 3 and left to stand overnight. The precipitate was collected and recrystallized from ethanol to give **8a** and **8b**.

8a: was obtained in 50% yield, m.p. 242–244°; IR: 3150 (NH), 1700 (C=O).
^{1}H NMR: 2.51 (t, 2H, SCH_2), 3.77 (t, 2H, NCH_2), 4.53 (s, 2H, OCH_2), 7.1–7.5 (m, 10H, Ar—H), 10.41 (s, 1H, NH)

Analysis: $C_{20}H_{18}N_6O_2S$ (406.458)
Calculated: C, 59.1; H, 4.46; N, 20.67
Found: C, 59.0; H, 4.3; N, 20.5

8b: was obtained in 53% yield, m.p. 223–225°; IR: 3150 (NH), 1705 (C=O)
^{1}H NMR: 1.71 (m, 2H, CCH_2C), 2.38 (t, 2H, SCH_2), 3.71 (t, 2H, NCH_2), 4.55 (s, 2H, OCH_2), 7.1–7.5 (m, 10H, Ar—H), 10.43 (s, 1H, NH).

Analysis: $C_{21}H_{20}N_6O_2S$ (420.485)
Calculated: C, 59.98; H, 4.79; N, 19.98
Found: C, 59.8; H, 4.8; N, 19.8

3-(Carboxymethylthio)-5[(5,6-diphenyl-1,2,4-triazin-3-yl)oxymethyl]-s-triazole (**9**). Compound **3** (0.1 mole) and chloroacetic acid (0.11 mole) in 10% aqueous sodium hydroxide (50 ml) were heated on a steam bath for two hours. The reaction mixture was cooled and acidified with acetic acid to give 9 in 80% yield, m.p. 190–192° (decomp).

IR: 3320 (NH), 3100–3000 (OH), 1730 (C=O).
Analysis: $C_{20}H_{16}N_6O_3S$ (420.434)
Calculated: C, 57.13; H, 3.83; N, 19.98
Found: C, 57.0; H, 3.9; N, 19.7

2-[(5,6-Diphenyl-1,2,4-triazin-3-yl)-oxymethyl]-5,6-dihydrothiazolo[3,2-b]-s-triazol-6-one (**10**). Compound **9** (5 g), pyridine (2 ml) and acetic anhydride (10 ml) were heated on a steam bath for two hours, then cooled. The precipitated solid was filtered, washed well with water and recrystallized from ethanol to give 10 in 60% yield, m.p. 150°.
IR: 1720 (C=O). ^{1}H NMR 4.35 (s, 2H, S—CH_2), 4.73 (s, 2H, OCH_2), 7.1–7.5 (m, 10H, Ar—H).

Analysis: $C_{20}H_{14}N_6O_2S$ (402.426)
Calculated: C, 59.69; H, 3.50; N, 20.88
Found: C, 59.5; H, 3.4; N, 20.7

2-[(5,6-Diphenyl-1,2,4-triazin-3-yl)oxymethyl]-5-benzylidene-5,6-dihydrothiazolo-[3,2-b]-s-triazol-6-one (**11**). Compound **10** (0.01 mole), benzaldehyde (0.01 mole) and sodium acetate (0.03) in ethanol (25 ml) were refluxed for 6 hours then cooled. The solid obtained was filtered, washed with cold water and recrystallized from ethanol to give 11 in 45% yield, m.p. 228–230°.

IR: 1730 (C=O). ^{1}H NMR 4.88 (s, 2H, OCH_2), 6.10 (s, 1H, =CH), 7.0–7.8 (m, 15H, Ar—H).
Analysis: $C_{27}H_{18}N_6O_2S$ (490.53)
Calculated: C, 66.11; H, 3.69; N, 17.31
Found: C, 66.0; H, 3.5; N, 17.4

2-[(5,6-Diphenyl-1,2,4-triazin-3-yl)oxymethyl]-6-phenyl-thiazolo[3,2-b]-s-triazole (**12**). Compound **3** (0.01 mole), phenacyl bromide (0.1 mole) and anhydrous sodium acetate (0.03 mole) were heated in absolute ethanol (40 ml) under reflux for ten hours. The mixture was cooled, diluted with enough water to develop turbidity and left overnight in a refrigerator for complete separation of the product. The crude product was crystallized from ethanol to give 12 in 50% yield, m.p. 163–165°; ^{1}H NMR: 4.8 (s, 2H, OCH_2), 6.8 (s, 1H, =CH—, methine proton of the thiazole ring), 7.1–7.9 (m, 15H, Ar—H).

Analysis: $C_{26}H_{18}N_6OS$ (462.525)
Calculated: C, 67.51; H, 3.92; N, 18.16
Found: C, 67.4; H, 3.8; N, 18.0

Biological Tests: Carried out by applying the ager Plate diffusion technique.[12] All of the newly synthesized compounds were screened in vitro for antibacterial and antifungal activity against Staphylococcus aureus, Escherichia coli and Candida albicans. In this method a standard 6 mm agar plate discs impregnated with the test compound (1 mg/ml of acetone) were used. Penicillin V sodium salt, was used as a positive control. The plates were incubated for 24 hours at 37°. The zone of inhibition of bacterial growth (mm) around the disc was observed. The screening results indicated that none of the tested compounds showed any noteworthy activity, against the control which showed a zone of inhibition of bacterial growth equal 83 mm (Staphylococcus aureus) and 17 mm (Escherichia coli).

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