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Efficient synthesis and anti-oxidant evaluation of some new 1-(2-phenothiazinyl)-3-aryl-2-propen-1-one derivatives

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Abstract

Commercial available lithium hydroxide monohydrate $LiOH.H_2O$ was applied as a 'dual activation' catalyst leading to an efficient Claisen–Schmidt condensation between 2-acetylphenothiazine and aromatic aldehydes. The 1-(2-phenothiazinyl)-3-aryl-2-propen-1-ones **(3)** was obtained at 80 ^{0}C in a short reaction time and high yield. The antioxidant activity of the synthesized compounds was evaluated. Compounds **3a, 3e** and **3h** were found to be with a high potent anti-oxidants activiy. Also, compounds **3a, 3e** and **3h** have an ability to protect DNA from the induced damage by Bleomycin.

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Introduction

Some 1-(2-phenothiazinyl)-3-aryl-2-propen-1-ones have been recently reviewed and showed considerable biological activities (Upadhyay et al., 2009). Furthermore, some of their structures containing, pyrimidine, pyrimidinethione, pyridine and pyrazolone rings were previously obtained from these compounds. (Zoorob et al., 1981& Bansode Et al.2012). Also, the literature showed that the derivatives 2-(2-amino-6-aryl-4-pyrimidinyl) and 2-(5-aryl-4,5-dihydro-3-pyrazolyl) phenothiazines have anti-inflammatory active (Sawhney et al., 1988).

The synthesis of 1-(2-phenothiazinyl)-3-aryl-2-propen-1-ones has generated vast interest to organic/medicinal chemists. The convenient approach synthesis of 2-cinnamoylphenothiazines involves Claisen–Schmidt condensation of 2-acetylphenothiazine with aldehydes. The reaction was catalysed by high concentrated NaOH solution (Zoorob et al., 1981& El-Rayyes, 1982). The reported procedures have various disadvantages such as long reaction times (6-8 h) and high concentration of NaOH (Zoorob et al., 1981& Sawhney et al., 1988). Recently, Bhagat *et al.* reported the use of $LiOH{\cdot}H_2O$ as a 'dual activation' catalyst for Claisen–Schmidt condensation of aryl methyl ketones with aryl/heteroaryl aldehydes for easy synthesis of 1,3-diaryl-2-propenones under mild condition (Bhagat *et al.*, 2006).

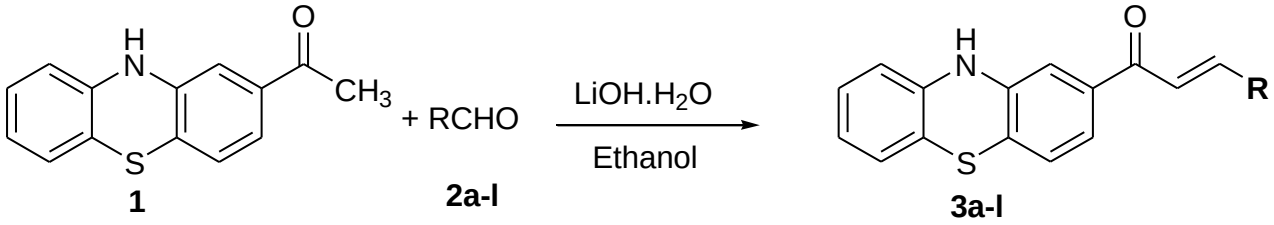
On the other hand, oxidative stress results in oxidative alteration of biological macromolecules such as lipids, proteins and nucleic acids. It is considered to play a pivotal role in the pathogenesis of aging and degenerative diseases (Gutteridge, 1993,

Kehrer, 1993& Becker, 2004). In order to cope with an excess of free radicals produced upon oxidative stress, human bodies have developed sophisticated mechanisms for maintaining redox homeostasis. These protective mechanisms include scavenging or detoxification of reactive oxygen species (ROS), blocking ROS production, sequestration of transition metals, as well as enzymatic and nonenzymatic antioxidant defences produced in the body, that is, endogenous (Hayes, 1999 & Masella, 2005), and others supplied with the diet, namely, exogenous ones. Among them, dietary polyphenols have been widely studied for their strong antioxidant capacities and other properties by which cell functions are regulated (Hartmann, 2006 & Hollman 1997). In view of the above results, we report herein for the using of LiOH·H_2O as a 'dual activation' catalyst for Claisen–Schmidt condensation of 2-acetylphenothiazine with aldehydes for efficient synthesis of 2-cinnamoylphenothiazines and evaluate of their anti-oxidant activities properties.

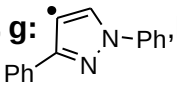
Results and Discussion

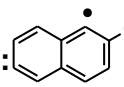
This work was based on the initiation of the reaction between benzaldehyde with 2-acetylphenothiazine **1** in a variety concentration of LiOH.H_2O (0.5, 1.0, 1.5, 2.0, 2.5 mmol) in ethanol yield compound **3a** in 99% yield rather than the previously recorded 90% by NaOH. Also, the influence of reaction time on the same reaction was investigated. The results obtained in short time . Trials check the generality of using LiOH.H_2O as catalytic system for condensation of 2-acetylphenothiazine (2 mmol) with various aryl aldehydes **2a-h** (2 mmol) under the catalytic influence of LiOH.H_2O (2,4 or 6 mmol) were implemented as in Table 1. Excellent to good results, yields (99% for **3a**) were obtained and the reactions were completed after 10-30 min. The reactions could be monitored visually where the propenone derivatives **3k-l** were precipitated out in the reaction medium due to their poor solubility in ethanol. Thus, the formation of a yellow or light orange precipitate indicates completion of the reaction (Scheme1).

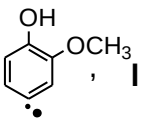
Scheme 1: Synthesis of 1-(2-Phenothiazinyl)-3-aryl-2-propen-1-ones **3a-l**

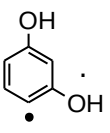


R= a: C_6H_5, **b:** 4-Me-C_6H_4, **c:** 4-Cl-C_6H_4, **d:** benzo[*d*][1,3]dioxole-5-yl, **e:** 4-N$(CH_3)_2$ -C_6H_4,

f: styryl, **g:** 

h: 4-MeO-C_6H_4, **i:** 2-OH-C_6H_4 **j:** 

, **k:** 

, **l:** 

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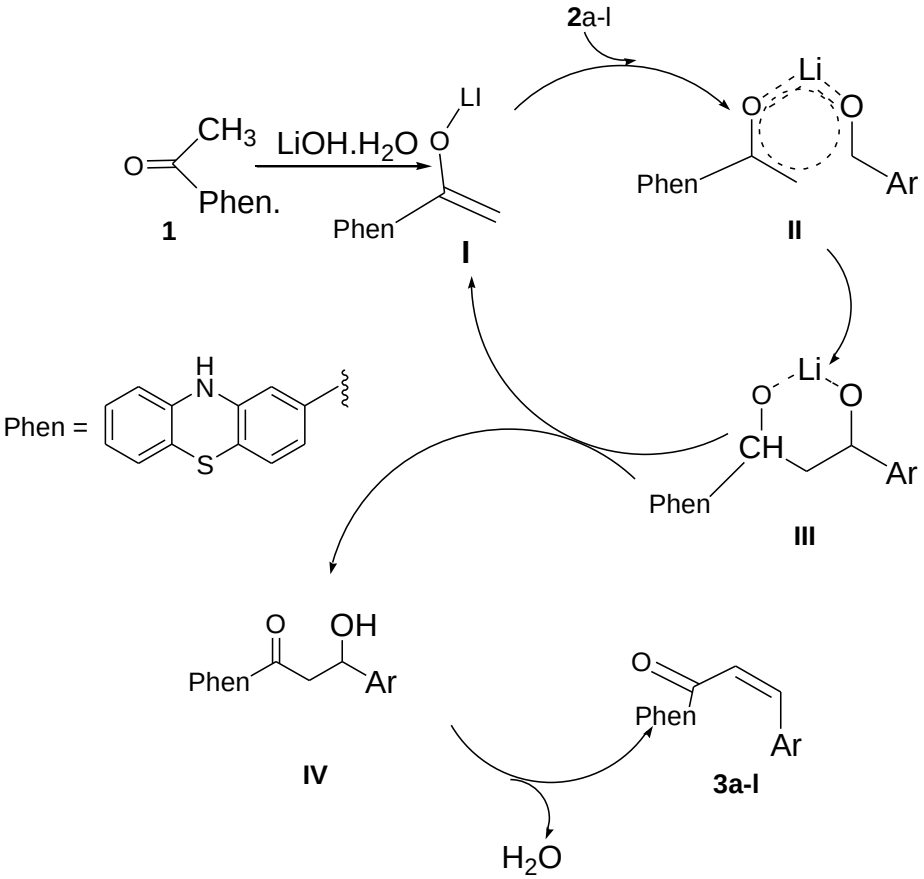
The dual role of LiOH.H_2O appears in generation of the enolate from the 2-acetylphenothiazine in addition to the activating carbonyl of aldehyde by coordination with Li^+ as demonstrated in Fig. 1. Proton abstraction from **1** by LiOH.H_2O catalyst generates the lithium enolate **I.** Coordination of the Li+ of I with the aldehyde carbonyl oxygen forms the six-membered cyclic transition state **II**, increases the electrophilicity of the aldehyde carbonyl group and makes it more susceptible to nucleophilic attack in an intramolecular fashion to form the enolate anion **III**. The enolate anion **III** subsequently hydrolyzed by water under the reaction conditions and generates enolate **IV** and LiOH to complete the catalytic cycle. Further dehydration of **IV** results in the formation of 2-cinnamoylphenothiazines **3a-l** Fig. 1. This proposed mechanism was based on

Bhagat et al. (2006) postulation for the similar reaction conditions (figure1).

The chemical structures of the newly synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral and elemental analysis (c.f. Experimental part).

Fig. 1:- A suggested mechanism of using $LiOH.H_2O$ in condensation reaction of **3**



Experiments

Chemistry

All melting points are given in degree Celsius (uncorrected) and were determined on a Gallenkamp electric melting point apparatus. Thin-layer chromatography (TLC) was carried out on silica gel 60 F254 precoated aluminum sheets. The IR spectra were recorded (KBr) on a Mattson 5000 FTIR spectrophotometer (ν, cm^{-1}) at Microanalytical Unit, Faculty of Science, Mansoura University. The ^{1}H NMR spectra were carried out on a Varian spectrophotometer at 300 MHz using tetramethyl silane (TMS) as an internal reference and DMSO-*d6* and deutrated chloroform as solvents, at Microanalytical Center, Cairo University. The mass spectra (EI) were recorded on a Varian Star 3400 Cx ion trap GC/MS Shimadzu GCMS-QP 5050 A EI (70 eV) at the Regional Center for Mycology and Biotechnology, Al-Azhar University. Elemental analyses (C, H, and N) were carried out at Microanalytical Center, Cairo University, Giza, Egypt. The results of the elemental analysis were found to agree favorably with the calculated values. Biological activity determinations were carried out at the Pharmacognosy Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

Synthesis of 1-(2-phenothiazinyl)-3-aryl-2-propen-1-ones (3a-h):

General procedure

2-Acetylphenothiazine **1** (0.48 g, 2 mmol) in ethanol (15 mL) was treated with $LiOH.H_2O$ (0.08 g, 2 mmol for **3a-g**; 0.17g, 4mmol for **3h-j** and 0.24g, 6mmol for **3k-l**) followed by

addition of the appropriate aromatic aldehyde (2 mmol). The reaction mixture was refluxed on a water bath for 30 min. After the reaction was completed, a precipitate was filtered off and recrystallized from appropriate solvent to give the pure product **3**.

1-(2-phenothiazinyl)-3-aryl-2-propen-1-ones (3a-c,e and h):

The experimental data for compounds **3a-c,e and h** were listed in table 1 and are consistent with published for each compounds procedure (cf. Table 1).

Table 1: Charactrization of **3a-l** obtained by condensation in presence of $LiOH.H_2O$

Comp. No	Conc.mmol ($LiOH.H_2O$)	Yield time ($LiOH.H_2O$)/	M.p	Lit.M.p
3a	1	99%/10min	200°C	199°C (Zoorob1981)
3b	1	88 %/30 min	170°C	170°C (Sawhney 1988)
3c	1	85%/30 min	214°C	212°C (Sawhney 1988)
3e	1	82%/30min	117°C	115 °C (Lissi 1999)
3h	2	94%/30 min	195°C	193°C (Zoorob1981)

3-(Benzo[d][1, 3] dioxol-5-yl)-1-(10H-phenothiazin-8-yl) prop-2-en-1-one(3d). Yield, 63 %, reddish brown powder; m.p.; 200-201°C; Crystalization solvent, ethanol; R_f = 0.7 [pet. ether (40:60): ethyl acetate (4:1)]; IR (KBr): ν_{max}, cm^{-1}: 3338 (NH), 1646 (CO), 1599 (C=C); ^1H NMR (300 MHz, DMSO-d_6) δ: (ppm) 6.09 (s, 2H, CH_2), 6.63-7.69 (m, 12H, ArH, CH=CHC=O), 8.77 (s, 1H, NH). MS (EIMS) *m/z* (%):375 (M^++2, 5.7), 374 (M^++1, 13.9), 373 (M^+, 100%), 121 (5.2), 78 (1.1), 134 (0.8), 135 (1.7), 198 (38.5), 226 (3.5), 254 (12.6), 241 (3.1); Anal. Calcd. for $C_{22}H_{15}NO_3S$ (373.08), C, 70.76; H, 4.05; N, 3.75. Found: C, 70.52; H, 4.18; N, 3.6.

1-(10H-Phenothiazin-8-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one (3g), Yield 84%, red powder; m.p.; 221-222°C; Crystalization solvent, ethanol; R_f = 0.8 [pet. ether (40:60): ethyl acetate (4:1)]; IR (KBr): ν_{max}, cm^{-1}: 3335 (NH), 1647 (CO), 1586 (C=C); ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.70-7.96 (m, 19H, Ar-H, CH=CH), 8.80 (s, 1H, NH), 9.38 (s, 1H, CH). MS (EIMS) *m/z* (%): 375 (M^++2, 5.7), 374 (M^++1, 13.9), 373 (M^+, 100%), 121 (5.2), 78 (1.1), 134 (0.8), 135 (1.7), 198 (38.5), 226 (3.5), 254 (12.6), 241 (3.1). Anal. Calcd. for $C_{30}H_{21}N_3OS$ (471.14), C, 76.41; H, 4.49; N, 8.91. Found: C, 76.30; H, 4.55; N, 8.77.

3-(2-Hydroxynaphthalen-1-yl)-1-(10H-phenothiazin-8-yl) prop-2-en-1-one (3j), Yield 60%, brown powder; m.p. > 300 °C; Crystalization solvent, ethanol; *R_f = 0.65 [pet. ether (40:60): ethyl acetate (4:1)];* IR (KBr): ν_{max}, cm^{-1}: 3380, 3347 (OH, NH), 1646 (CO), 1569 (C=C); ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.21 (br, 1H, OH), 6.63-7.43 (m, 15H, ArH, CH=CH), 8.74 (br, 1H, NH). MS (EIMS) *m/z* (%): 396 (M^++1, 8.7%), 395 (6.0%), 198 (100), 226 (7.6), 241 (21.9), 156 (11.3%), 169 (8.0%), 197 (71.2), 54 (12.8), 78 (17.2); Anal. Calcd. for $C_{25}H_{17}NO_2S$ (395.1), C, 75.93; H, 4.33; N, 3.54. Found: C, 75.65; H, 4.41; N, 3.49.

3-(2-Hydroxyphenyl)-1-(10H-phenothiazin-8-yl) prop-2-en-1-one: (3i),

Yield 63 %, brown powder; m.p. > 300 °C; Crystalization solvent, ethanol; *R_f = 0.75 [pet. ether (40:60): ethylacetate(4:1)];* IR (KBr): ν_{max}, cm^{-1}: 3426, 3405 (NH, OH), 1660 (CO), 1594 (C=C); ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.30 (br, 1H, OH), 6.65-7.94 (m, 13H, ArH, CH=CH), 8.70 (br, 1H, NH). MS (EIMS) *m/z* (%): 345 (M^+, 4.5), 57 (100), 93 (8.5), 107 (10.7), 119 (5.2), 120 (5.4), 90 (26.9), 91 (17.8); Anal. Calcd. for $C_{21}H_{15}NO_2S$ (345.08), C, 73.02; H, 4.38; N, 4.06 Found: C, 73.14; H, 4.52; N, 4.18.

3-(3-Hydroxy-4-methoxyphenyl)-1-(10H-phenothiazin-8-yl) prop-2-en-1-one (3k), Yield 61 %, dark brown; m.p. > 300 °C*;* Crystalization solvent, ethanol; R_f =0.77 [pet. ether (40:60): ethyl acetate (4:1)]*;* IR (KBr): ν_{max}, cm^{-1}: 3384, 3347 (OH, NH), 2925, 2898, 2975 (CH aliphatic), 1646 (CO) ; ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 3.85 (s, 3H, OCH_3), 6.20 (br, 1H, OH), 6.65-7.93 (m, 12H, ArH, CH=CH), 8.76 (br, 1H, NH. MS (EIMS) *m/z* (%): 377 (M^++2, 1.1), 375 (M^+, 1.3%), 252 (0.9), 123 (3.7), 54 (37.2), 57 (100%), 198 (4.4%), 199 (2.0%), 78 (7.5), 358 (0.8%), 359 (0.7), 343 (1.0), 176 (1.8), 177 (1.3), 148 (2.9), 149 (2.3), 135 (3.4), 136 (1.6), 225 (3.7), 226 (1.7), 227 (1.5); Anal. Calcd. For $C_{22}H_{17}NO_3S$ (375.09), C, 70.38; H, 4.56; N, 3.73 Found: C, 70.53; H, 4.48; N, 3.62.

3-(2, 4-Dihydroxyphenyl)-1-(10H-phenothiazin-8-yl) prop-2-en-1-one (3l), Yield 64%, dark orange; m.p. > 300 °C*;* Crystalization solvent, ethanol; *R_f = 0.68 [pet. ether (40:60): ethyl acetate (4:1)];* IR (KBr): ν_{max}, cm^{-1}: 3382 (br, 2OH, NH), 1660 (CO); ^1H NMR (DMSO-d_6): δ (ppm) 6.20 (br, 2H, 2OH), 6.64-6.98 (m, 12H, ArH, CH=CH). MS *m/z* (%):358 (M^+-3H, 2.9), 198 (2.0), 54 (33.9), 76 (100%), 78 (21.3), 226 (1.3), 109 (12.3), 122 (8.0), 135 (7.4), 176 (1.6), 327 (2.2), 356 (13.1), 119 (37.5), 163 (3.3), 92 (11.6), 105 (10.7); Anal. Calcd. for $C_{21}H_{15}NO_3S$ (361.08), C, 69.79; H, 4.18; N, 3.88. Found: C, 69.56; H, 4.22; N, 3.79.

Biology

ABTS Antioxidant assay

The antioxidant activity of the synthesized compounds was evaluated using the procedure developed by Lissi et al (1999). Some of the 1-(2-phenothiazinyl)-3-aryl-2-propen-1-ones exhibited antioxidant activity as shown in (Table 2). Compared with the control (L-ascorbic acid), the antioxidant potency of compounds 3a, 3e and 3h were found to be high, while compounds **1**, **3b**, **3c** and **3i** showed moderate antioxidant activity and the rest of tested compounds showed weak activities. **3a, 3b, 3e** and **3h** were more potent than the starting material. From the structure activity relationships (SAR) we found that, the presence of cinamoyl, N $(CH_3)_2$-cinnamoyl, 4-MeO-cinnamoyl, OH-cinnamoyl, pyrazole, naphthol moieties incorporated with the phenothiazine skeleton enhanced the antioxidant activity.

Table 2: ABTS Antioxidant activity assay for 1-(2-phenothiazinyl)-3-aryl-2-propen-1-one

No.	Compounds	Absorbance of samples	Inhibition%
	Control	0.516	0%
	L-Ascorbic-acid	0.038	92.63%
1	1	0.152	70.25%
2	3a	0.049	90.39%
3	3b	0.123	76.16%
4	3c	0.202	60.85%
5	3d	0.366	29.06%
6	3e	0.046	91.08%
7	3f	0.180	65.11%
8	3g	0.229	55.62%
9	3h	0.082	84.10%
10	3i	0.158	69.36%
11	3j	0.351	31.97%
12	3k	0.342	33.72%
13	3l	0.265	48.64%

Bleomycin-dependent DNA damage

Damage to DNA in the presence of a Bleomycin-Fe complex F has been adopted as a sensitive and specific method to examine stimulated, resulting in a positive test for pro-oxidant activity. DNA degradation is accompanied by the formation of a product similar to malondialdehyde (MDA). L-Ascorbic acid, a reducing agent, can reduce Fe^{3+} to Fe^{2+} (Table 3) shows that, compounds **3a**, **3b**, **3e** and **3h** possess high pro-Potential pro-oxidant agents (Gutteridge et al.1981). If the samples to be tested are able to reduce the bleomycin-Fe^{3+} to Bleomycin-Fe^{2+}, DNA degradation in this system will be

antioxidant action compared to the L-ascorbic acid, whereas the rest of tested compounds showed weak activities. Furthermore, **3a** and **3e** were more potent than L-Ascorbic acid. Moreover, **3a**, **3e** and **3h** were more potent than the starting material **1** .

Table 3. Assays for bleomycin-dependent DNA damage of the investigated compounds **3a-l**

No.	Compounds	Absorbance of samples	Activity%
	Control	0.435	0%
	L-Ascorbic-acid	0.081	81.3%
1	**1**	0.095	%78.1
2	**3a**	0.081	81.3%
3	**3b**	0.099	77.2%
4	**3c**	0.133	69.4%
5	**3d**	0.137	68.5%
6	**3e**	0.078	82.0%
7	**3f**	0.117	73.1%
8	**3g**	0.128	70.5%
9	**3h**	0.083	80.9%
10	**3i**	0.110	74.7%
11	**3j**	0.138	68.2%
12	**3k**	0.142	67.3%
13	**3l**	0.131	69.8%

All compounds were dissolved in DMSO/MeOH (1:1) and tested at the final concentration of (0.1 mL of 1 mg/mL). The extent of DNA damage is expressed by increase in absorbance at 520 nm. The values are mean ±SD (n= 3).

Conclusion

In conclusion, we have used $LiOH.H_2O$ as a novel dual activation catalyst for Claisen–Schmidt condensation of 2-acetylphenothiazine with aldehydes, as an easy way to synthesize 2-cinnamoylphenothiazines. The advantages of using $LiOH.H_2O$ are (i) cheap and easily available, (ii) short reaction times (iii) high product yields and (iv) clean product. Compounds **3a**, **3b**, **3e** and **3h** exhibited high antioxidant activity when compared to L-ascorbic acid; these compounds also showed the best protective effect against DNA damage induced by Bleomycin .

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التشييد الفعال والكفاءة المضادة للأكسدة لبعض مشتقات ١ -(٢ -فينوثيازينيل)-٣ -أريل-٢ -بروبين-١ -أحادي

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هيدروكسيد الليثيوم أحادي الماء المتاح تجاريا تم استخدامه كحافز مزدوج النشاط يؤدي الي التكثيف الفعال لتفاعل كليزن- شميدت بين 2- أسيتيل فينوثيازين والألدهيدات الأروماتيه. 1- (2-فينوثيازينيل)-3- أريل-2- بروبين-1-أحادي (**3**) تم الحصول عليه عند درجة حرارة ٨٠ درجه مئويه في وقت تفاعل قصير وكمية عالية. تم تقييم النشاط المضاد للأكسده للمواد التي تم تحضيرها. المركبات **3a, 3e** and **3h** وجد لها نشاط بيولوجي فعال وأيضا لها قابليه لحماية الحمض النووي DNA من التلفيات الحاصله بالبليوميسين.