مجلة العلوم البحثة والتطبيقية
Journal of Pure & Applied Sciences
www.Suj.sebhau.edu.ly ISSN 2521-9200
Received 11/05/2018 Revised 09/12/2018 Published online 14/12/2018

Computational Study for some synthesised derivatives of mono and di-[(E) -1-phenylmethylene]-1-cyclohexanone and their biological activities

*Arabya A. A. Almutaleb[1] , Boubaker M. Housouna[1] and Huda S. Alrawig[2]
[1]Chemistry department, Faculty of Science, Sebha University, Libya
[2] Botany department, Facutly of Science, Sebha University, Libya
*Corresponding author: Ara.almagraby@sebhau.edu.ly

Abstract The principal interest in our study is computational study, for a variety of conjugated Ketones such as mono and diarylidene cyclohexanones, using molecular modeling calculation. The molecular modeling study adopted was quantum mechanics calculation using Gaussian 03 software. The quantum mechanics calculations performed using the semi empirical method PM3. The synthesis route had been done through the reactions of some aromatic aldehydes derivatives with cyclohexanone. The mechanism of the formation of the products were discussed. The structure of the synthesized compounds has been confirmed by analytical and spectral methods (IR, 1HNMR and mass spectra) in addition to the elemental analysis (C, H, N). The resulting compounds was applied to the biological activity, which indicates different effects on different kinds of bacteria.

Keywords: Cyclohexanone, mon-, diarylidine, computational, bacteria.

دراســـــة حوسبية لبعض الشتقات المخلقة من أحادي وثنائي-(E)-1-فينايل ميثيلين-1-هكسانون حلقي وتأثيراتها البيولوجية

*عــربية المطلب[1] و أبوبكر حسونة[1] و وهدى الرويق[2]
[1]قسم الكيمياء- كلية العلوم- جامعة سبها، ليبيا
[2] قسم النبات- كلية العلوم- جامعة سبها، ليبيا
*للمراسلة: Ara.almagraby@sebhau.edu.ly

الملخــص الهدف من دراستنا هو دراسة حوسبية لعدد من الكيتونات المتعاقبة مثل، أحادي وثنائي آريليدين هكسانون حلقي، باستخدام نماذج حوسبية جزيئية. العرض الجزيئي للدراسة كان حساب ميكانيكيات الكم باستخدام معالج جوسيان 03. حسابات ميكانيكة الكم اعتمدت باستخدام طريقة MP3 التجريبية. تم تخليق المركبات العضوية من خلال تفاعل بعض مشتقات الألديهيدات الأروماتية مع الهكسانون الحلقي. تم استعراض وشرح ميكانيكية التفاعلات خلال الدراسة. أجريت التحاليل الطيفية باستخدام طيف الأشعة تحت الحمراء، طيف الرنين النووي المغناطيسي ومطياف الكتلة بالإضافة إلى التحليل العنصري (كربون، هيدروجين ونيتروجين). أخضعت المركبات الناتجة للدراسة البيولوجية، حيث تم إختبار تأثيراتها على عدة أنواع من البكتيريا وبينت النتائج تأثيرات مختلفة.

الكلمات المفتاحية: أحادي، ثنائي – آريليدين، بكتيريا، حوسبية، هكسانون حلقي.

Introduction

Computational chemistry is prompting an extensive variety of possibilities usually interdisciplinary due to explosive increase in computer power and software capabilities. Computational chemistry is additionally coordinating the science educational modules[1].

A second use of computational chemistry is the understanding of problem more completely. Many experimental chemists are now using computational chemistry technique to gain additional understanding of the compounds being examined[2]. Despite their ubiquity and utility in organic chemistry, the synthesis of α, β-unsaturated carbonyl compounds is often a tedious and sometimes challenging transformation. Several methods to effect this operation have been developed over the years[3]. Condensation of 2-acetylfuran or 2-acetylthiophene with different aromatic aldehydes in alcoholic sodium hydroxide solution to give (E)-1-(furan-2-yl)-3-phenylprop-2-en-1-one **1** and (E)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one **2** has been reported[4].

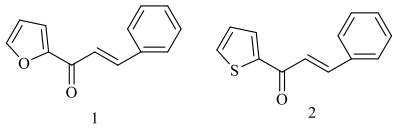
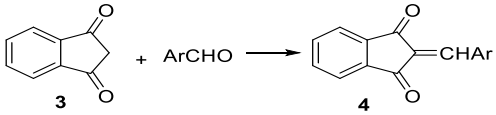
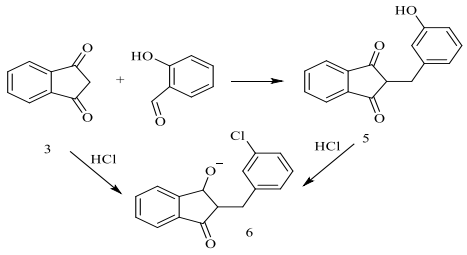


Figure 1
Condensation of indan-1,3-dione **3** with aromatic aldehydes under heating to approximately 110 °C or using condensing agent such as potassium hydroxide[5], piperidine[6] and acetic acid[7] gave 2-arylidine-indan-1,3-dione **4**.



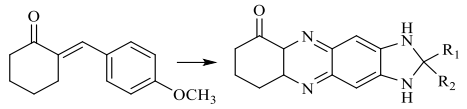
Scheme 1:
Condensation of indan-1, 3-dione **3** and salicylaldehyde in alcoholic KOH solution afforded the expected arylidine **5**, whilst the same condensation with dry HCl gave a

ketoindenopyranolhydrochloride **6** which can also be obtained by the action of dry HCl on arylidine **5**.



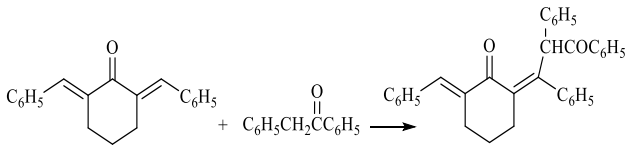
Scheme 2:

Arylidene cycloalkanones are frequently used *α, β*-unsaturated ketones. Their synthesis is based on the reaction of the appropriate cyclic ketone with aldehydes, through aldol condensation reaction. Several reports exist for their synthesis [8-13], involving the use of organic and inorganic bases, metal catalysts, and different types of Friedel-Crafts catalysts. The reaction of 2-arylidenecyclohexonone **7** (Ar = *p*-$C_6H_5OCH_3$) with *o*- phenylene diamine to give imidazophenazine **8** in (6-8 %) yield has been reported[14].



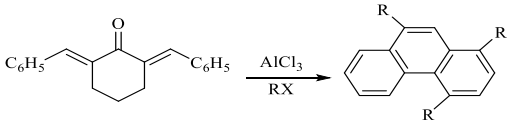
Scheme 3:

Reaction of 2,6-dibenzilidenes **9** with phenyl benzyl ketone afforded the mono adduct 1,5-diketone **10**[4].



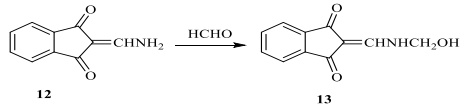
Scheme 4:

Reaction of 2, 6-dibenzilidenes **9** with anhydrous aluminium chloride and alkyl halide has been reported to give phenanthrene derivatives **11**[15].



Scheme 5:

Condensation of 2-aminomethylene indan-1,3-dione **12** with formaldehyde[16] afforded **13**.



Scheme 6:

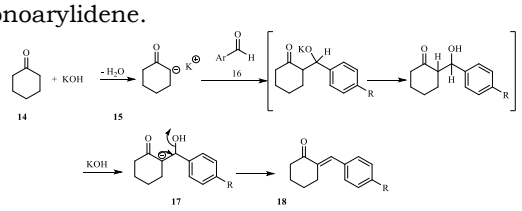
Computational chemistry utilized as a part of various diverse ways. One especially imperative route is to demonstrate model for a molecular system prior to synthesizing that molecule in the laboratory[17]. Although computational models may not be perfect, they are often good enough to rule out 90% of possible compounds as being unsuitable for their intended use. This is extremely helpful data because synthesising a single compound could require months of lab. work and raw materials, and generate toxic waste[18]. The goal of our study have been focussed on the application of a computational study on some mono- and diarylidine cyclohexanone derivatives and their biological activity.

1. Results and discussion:

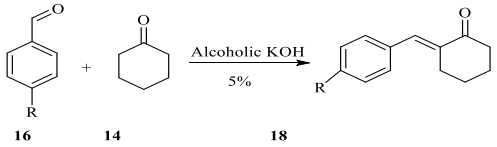
The derivatives of cyclohexanones constitute a very large and important class of carbocyclic chemistry; they far exceed in number the derivatives of any other alicyclic system. The reason for this is not far to seek; in addition to the usual methods of ring formation there exit in the case of the six-membered ring two highly convenient and widely applicable procedures the reduction of benzenoid compounds (whence derives the term "hydroaromatic" for this system) and the Diels-Alder synthesis, which cannot be employed for monocyclic systems of other sizes. In nature, also the preponderance of cyclohexanone derivatives over those of other alicyclic systems is overwhelming[19].

1.1. Derivatives of monoarylidine:

A more convenient method used solid potassium hydroxide [20,21] or sodium hydroxide [22] as a catalyst for the condensation of different aldehydes with cycloalkanones in ethanol gives an *α,α'-bis* (substituted benzylidene) cycloalkanones in good yields. The reactions were carried out at room temperature in basic medium by aldol condensation[23]. The aldol condensation between an aromatic aldehyde and an aliphatic ketone was first reported by Claisen and Claparede and simultaneously by Schmidt in 1881[24]. The 2-monoarylidenecyclohexanone was prepared during condensation reaction between cyclohexanone, by using a basic medium (alcoholic potassium hydroxide) to catalyse the reaction. In this reaction one molecule of an aromatic aldehyde combines with one molecule of the cyclohexanone, the basic catalyst removes a proton from one of the α-position of the aromatic aldehyde to form the aldol adduct, which spontaneously dehydrated to give the monoarylidene.



Scheme 7:



R= H

R= -$N(CH_3)_2$

Scheme 8:

1.2. Technical details

All calculations were done using an Intel CORE' i3 3.0 Hz workstation with double operating system and 64 bit Windows 7 'Labtop'. Quantum mechanics computational of complexes

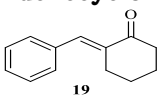
in vacuum were carried out using Gaussian 03[25]. Meanwhile the computational of complexes interface was performed using

Hyperchem molecular modeling software (Release 8.0). Minimization was performed using conjugate gradient algorithm with 0.1 k cal/Amol and further minimized at 0.01 k cal/ mol.

1.2.1. Quantum mechanics calculation

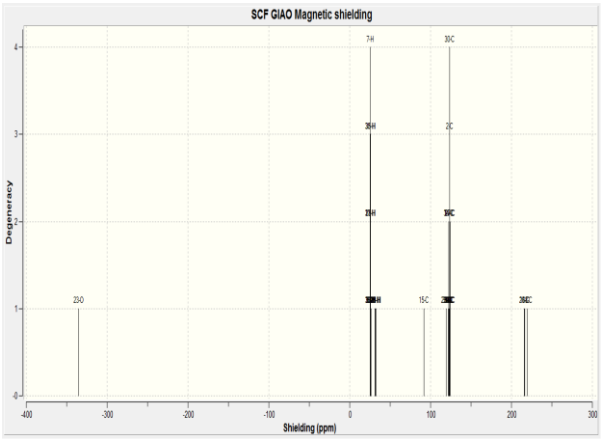
The starting geometries of Complexes structures were built based on the structures that were generated from the crystallographic parameters provided by the Cambridge Structural and were separately optimised using the semi empirical method, PM3 using Gaussian03 software package[25]. The starting geometries of the inclusion complexes were constructed using Hyper Chem. (Version 8.0, Hypercube, and Gainesville, FL, USA).

1.2.2. (E)-2-benzylidenecyclohexan-1-one



19

Figure 2:
Scan = -11.109743855 Kcal/mol, NMR= -356568.6785228 Kcal/mol, OPT+freq= -11.3810162589 Kcal/mol.



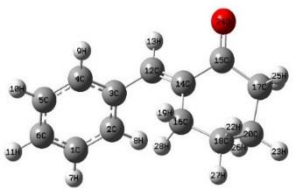


Figure 3: Crystal structure design for compound **19**

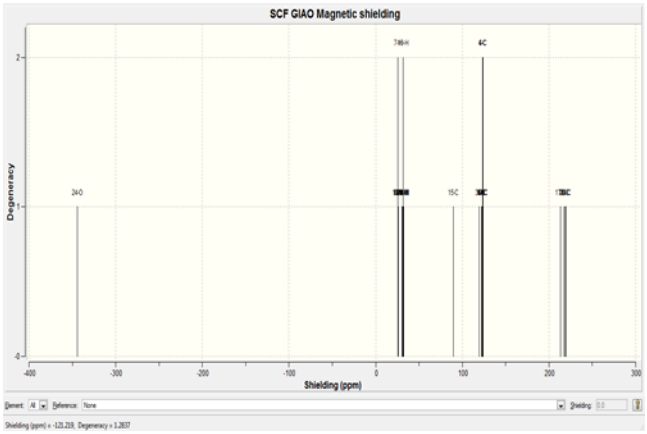
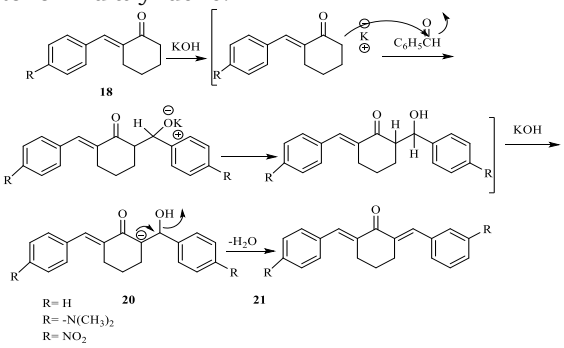


Figure 4: [1]HNMR design for compound **19**

1.3. Derivatives of the 2,6-di-((E)-benzylidene)cyclohexan-1-one

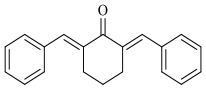
The derivatives of monoarylidene under the influence of the basic catalyst and in the presence of the aromatic aldehyde form the diarylidene derivatives. The reaction mechanism takes place by the nucleophilic attack at β-position for the cyclohexanone, whereas the presence of excess basic catalyst leads to eliminate a water molecule to form diarylidene.



18 20 21

Scheme 9:

1.3.1. 2,6-di((E)-benzylidene) cyclohexan-1-one



22

Figure 5: Scan = 35.4084219 Kcal/mol, NMR= -522301.7237 Kcal/mol., OPT+ freq.= 34.74897205 Kcal/mol.

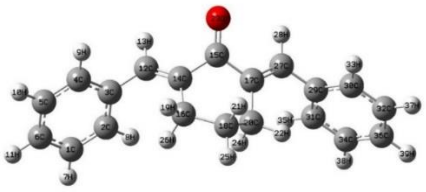
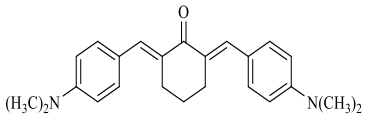


Figure 6: Crystal structure design for compound **22**

Figure 7: [1]HNMR design for compound **22**

1.3.2. 2, 6-bis ((E)-4-(dimethylamino) benzylidene)cyclohexan-1-one



23

Figure 8:
Scan = 30.73441659 Kcal/mol, NMR= -687298.2827837 Kcal/mol., OPT+ freq.= 29.5824972 Kcal/mol.

Figure 9: Crystal structure design for compound **23**

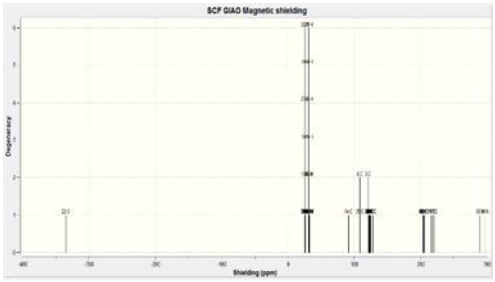
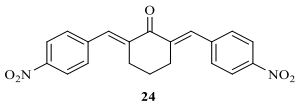


Figure 10: NMR design for compound **23**

1.1.1. 2, 6-bis ((E)-4-nitrobenzylidene) cyclohexan-1-one



24

Figure 11:
Scan = 20.11143193 Kcal/mol, NMR= -774169.5087285 Kcal/mol, OPT+freq= 17.8764937 Kcal/mol.

Figure 12: Crystal structure design for compound **24**

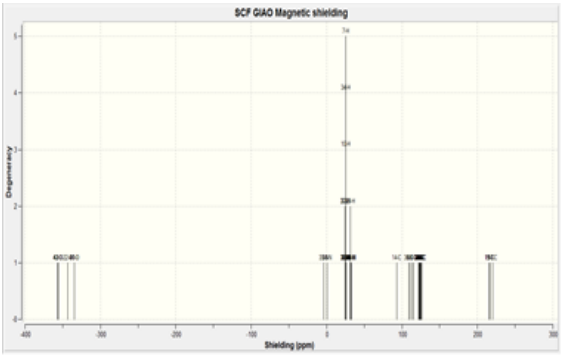
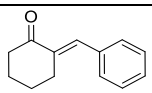
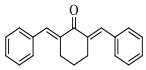
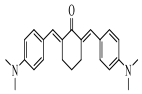
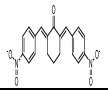


Figure 13: ^{1}HNMR design for compound **24**

1.2. Binding energy (kcal/mole):

Table 1: Binding energy (kcal/mole) for different compounds

Compound structure	Scan energy	NMR energy	Optimiz +freq energy
	-11.10974385	-356568.6785	-11.38101625
	35.4084219	-522301.723	34.74897205
	30.73441659	-687298.2827	29.5824972
	20.11143193	-774169.5087	17.8764937

2. Experimental

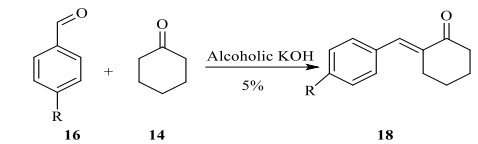
General Procedures

Starting materials were obtained from commercial suppliers and used without further purification.
NMR spectra were obtained as dilute solutions in the appropriate solvent at 25 ^{o}C. ^{1}H NMR and ^{13}C spectra were recorded on a Brücker DPX 400 MHz, AVIII 400 MHz, or Jeol EX 270 MHz spectrometer. All chemical shifts were recorded on the δ-scale using residual solvent as an internal standard ($CDCl_3$: δ_H 7.26, δ_C 77.16). All coupling constants are reported in hertz (Hz), and multiplicities were labeled s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), dd (double doublet), dt (double triplet), dq (double quartet).
Infrared spectra were recorded on a Perkin-Elmer 1600 FT spectrometer, as dilute solutions in $CHCl_3$.
Mass spectra were recorded using a Burker MicroTOF spectrometer using electrospray (ES^+) or (ES^-) or chemical ionisation techniques.

The reactions take place by condensation reaction between cyclohexanone and aromatic aldehyde derivatives by different ratio with stirring until the precipitate appears, after that the reaction mixture still for overnight. When the reaction was completed, we filtrate the precipitate then recrystallized it with the suitable solvent.

2.1. 2-[(E)-1-Phenylmethylene]-1-cyclohexanone

The ratio of the reaction was (1:1), 0.1 mole of cyclohexanone with 0.1 mole of aromatic aldehyde derivative in alcoholic medium (5%).

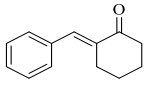


16 14 18

R= H
R= -N(CH$_3$)$_2$

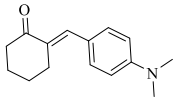
Scheme 10:

The structural formula was indicated by the spectral analysis as IR λ_{max}/cm^{-1} (CHCl$_3$), which shows absorption for the carbonyl group (C=O) 1660 cm^{-1}, methylene group (=CH) at 1420 cm^{-1} and the tertiary amine (-N (CH$_3$)$_2$) at 3400 cm^{-1}.



19

(E)-2-benzylidenecyclohexan-1-one, **19** Yellow solid, which was recrystallized from ethanol, 120-122 ^{o}C; δ_H (400MHz, CDCl$_3$), 7.55 (1H, s, Ar-CH), 7.51-7.26 (5H, m, ArH), 2.65 (2H, t, *J* = 7.5 Hz, CH$_2$), 2.43 (2H, t, *J* = 7.5 Hz, CH$_2$), 1.90 (2H, m, CH$_2$), 1.71 (2H, m, CH$_2$); δ_C (100 MHz, CDCl$_3$), 202.1 (C), 139.4 (C), 133.9 (C), 133.0 (CH), 130.8 (2CH), 129.1 (2CH), 128.3 (CH), 40.7 (CH$_2$), 29.4 (CH$_2$), 24.8 (CH$_2$), 24.0 (CH$_2$); *m/z* (HRMS-ESI+) C$_{13}$H$_{14}$O 186.1045 (M$^+$ C$_{13}$H$_{14}$O$^+$ requires 186.1065). *The elemental analysis:* calc. (C) 83.0%, (H) 7.5%, (O) 8.6%. Found: (C) 82.98%, (H) 7.35%, (O) 8.46%.

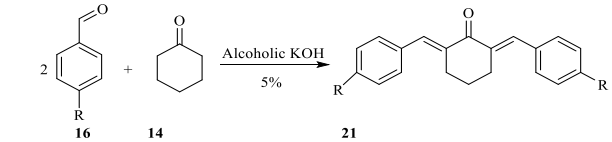


20

(E)-2-(4-(dimethylamino) benzylidene) cyclohexan-1-one 20 Yellowish orange solid, which was recrystallized from benzene, 142- 146 ^{o}C; δ_H (400MHz, CDCl$_3$), 7.54 (1H, s, Ar-CH), 7.39-7.29 (2H, m, ArH), 6.74 (2H, m, ArH), 3.04 (6H, s, 2CH$_3$), 2.65 (2H, t, *J* = 1.4 Hz, CH$_2$), 2.36 (2H, t, *J* = 3.5 Hz, CH$_2$), 1.79 (2H, m, CH$_2$), 1.60 (2H, m, CH$_2$); δ_C (100 MHz, CDCl$_3$), 201.9 (C), 151.9 (C), 135.5 (C), 135.1 (CH), 131.8 (2CH), 123.7 (C), 112.4 (2CH), 40.7 (CH$_2$), 40.0 (2CH$_3$), 29.4 (CH$_2$), 24.8 (CH$_2$), 24.0 (CH$_2$); m/z (HRMS-ESI+) C$_{15}$H$_{19}$NO 229.1467 (M$^+$ C$_{15}$H$_{19}$NO$^+$ requires 229.1465. *The elemental analysis:* calc. (C) 79.6%, (H) 7.07%, (O) 7.07%, (N) 6.19%. Found: (C) 79.82%, (H) 7.32%, (O) 6.09%, (N) 6.77%.

2.2. Di-[(E)-1-phenylmethylene]-1-cyclohexanone

The ratio of the reaction was (1:2), 0.05 mole of cyclohexanone with 0.1 mole of aromatic aldehyde derivative in alcoholic medium (5%).

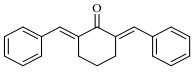


16 14 21

R= H
R= -N(CH$_3$)$_2$
R= -NO$_2$

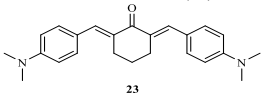
Scheme 11:

The structural formula was indicated by the spectral analysis as IR λ_{max} /cm^{-1} (CHCl$_3$), which shows an absorption for the nitro group (NO$_2$) at 1358 cm^{-1}, carbonyl group (C=O) 1664 cm^{-1}, tertiary amine (-N(CH$_3$)$_2$) 3400 cm^{-1}.



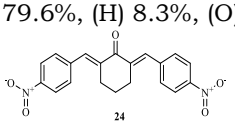
22

2,6 - di((E)-benzylidene) cyclohexan-1-one, **22**, Greenish yellow solid, which was recrystallized from ethanol, 162- 164 ^{o}C; δ_H (400MHz, CDCl$_3$), 7.68 (2H, s, Ar-H), 7.49 (8H, m, Ar H), 7.28 (2H, m, Ar H), 2.86 (2H, t, J=7.5, CH$_2$), 2.82 (2H, t, J = 7.5, CH$_2$), 1.85 – 1.73 (2H, m, CH$_2$); δ_C (100 MHz, CDCl$_3$), 190.3 (C), 136.8 (2C), 136.2 (2C), 128,8 (4CH), 128.5 (4CH), 128.3 (2C), 127.9 (2C), 29.4 (2CH$_2$), 25.1 (CH$_2$); *m/z* (HRMS-ESI+) C$_{20}$H$_{18}$O 274.1358 (M$^+$ C$_{20}$H$_{18}$O $^+$ requires 274.1360). *The elemental analysis:* calc. (C) 80.0%, (H) 7.7%, (O) 5.8%. Found: (C) 87.8%, (H) 7.2%, (O) 5.1%.



23

2, 6 -bis ((E)-4-(dimethylamino) benzylidene) cyclohexan-1-one, 23, Light orange solid, which was recrystallized from chlorobenzene, 152-154 ^{o}C; δ_H(400MHz, CDCl$_3$), 7.71 (2H, s, Ar-CH), 7.38-7.36 (4H, m, ArH), 6.75-6.70 (4H, m, ArH), 3.04 (12H, S, 4CH$_3$), 2.88-2.86 (4H, t, *J* = 1.4 Hz, 2CH$_2$), 1.80-1.7 9 (2H, m, CH$_2$); δ_C (100 MHz, CDCl$_3$), 192.0 (C), 151.9 (2C), 136.5 (2CH), 132.1 (2C), 132.0 (4CH), 129.3 (2C), 112.2 (4CH), 40.1 (4CH$_3$), 28.4 (2CH$_2$), 23.0 (CH$_2$); *m/z* (HRMS-ESI+) C$_{24}$H$_{28}$N$_2$O 360.2202 (M$^+$ C$_{24}$H$_{28}$N$_2$O $^+$ requires 360.2219). *The elemental analysis:* calc. (C) 87.5%, (H) 6.5%, (O) 4.4%, (N) 6.1%. Found: (C) 79.6%, (H) 8.3%, (O) 4.2%, (N) 7.8%.



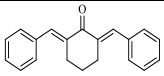
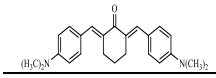
24

2,6-bis ((E)-4-nitrobenzylidene) cyclohexan-1-one, 24, Brown solid, which was recrystallized from ethanol, 205- 207 ^{o}C; δ_H(400MHz, CDCl$_3$), 8.44 (2H, d, J = 7.2 Hz, ArH), 8.41 (2H, d, *J* = 7.2 Hz, ArH), 7.80 (2H, s, Ar-CH), 7.57 (2H, d, *J* = 7.2 Hz, ArH), 7.55 (2H, d, *J* = 7.2 Hz, ArH), 2.97 (2H, t, *J* = 1.3 Hz, CH$_2$), 2.89 (2H, t, *J* = 1.3 Hz, CH$_2$), 1.79-1.77 (2H, m, CH$_2$); δ_C (100 MHz, CDCl$_3$), 192.0 (C), 147.5 (2C), 144.6 (2C), 139.2 (2C), 133.1 (2CH), 129.9 (4CH), 124.6 (4CH), 28.3 (2CH$_2$), 23.0 (CH$_2$); *m/z* (HRMS-ESI+) C$_{20}$H$_{16}$N$_2$O$_5$ 364.1059 (M$^+$ C$_{20}$H$_{16}$N$_2$O$_5$ $^+$ requires 364.1056). *The elemental analysis:* calc. (C) 65.9%, (H) 4.4%, (O) 22.0%, (N) 7.6%. Found: (C) 63.5%, (H) 4.7%, (O) 23.9%, (N) 7.7%.

3. Biological Activity

Based on the previous studies for the biological role for phenyl cyclohexanone derivatives as antifungal, we tested the biological effects for previous products on several kinds of bacteria[25] the result is illustrated as, for bacteria, *Bacillus subtilus* of the radius of the inhibitor activity areas were between 30-33 mm, and the two samples shown in (Table 2) gave the best result.

Table 2: Biological effect for different compounds

Structural formula for the products	Solvents	Biological effect	Radius of the Inhibitor activity area
	Cyclohexanone	+++	30 mm
	Cyclohexanone	+++	33 mm

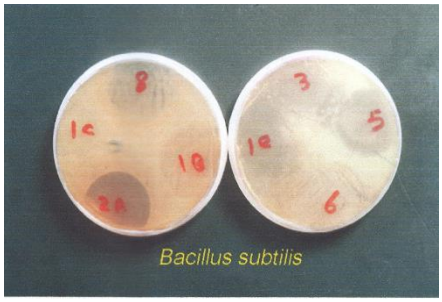
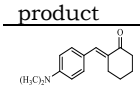
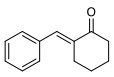


Figure 14: Picture for the effect of different compounds on bacteria, *Bacillus subtilus.*
For bacteria, *Pseudomonas fluorescens* the radius of the inhibitor activity areas were between 15-33 mm, where the first sample shown in (Table 3) had the lowest effect by 15 mm for the deactivated radius areas.

Table 3: Biological effect for different compounds

Structural formula for the product	Solvents	Biological effect	Radius of the inhibitor activity area
	Cyclohexanone	++	15 mm
	Cyclohexanone	+++	20 mm

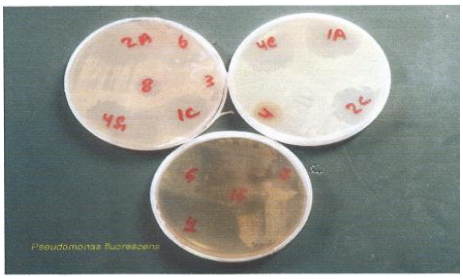
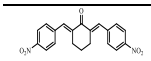
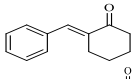
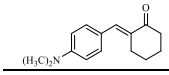


Figure 15: Picture for the effect of different compounds on bacteria, Pseudomonas fluorescens.
For bacteria, *Proteus vulgaris* the radius of the inhibitor activity areas were between 15-25 mm.

Table 4: Biological effect for different compounds

Structural formula for the products	Solvents	Biological effect	Radius of the inhibitor activity area
	Cyclohexanone	++	15 mm
	Cyclohexanone	+++	20 mm
	Cyclohexanone	+++	25 mm

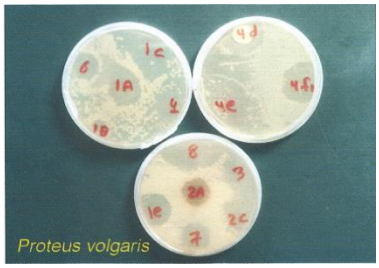
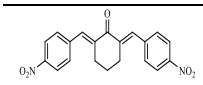
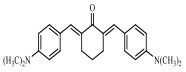


Figure 16: Picture for the effect of different compounds on bacteria, *Proteus vulgaris.*
For bacteria, *Micrococcus sp* the radius of the inhibitor activity areas were between 5-32 mm.

Table 5: Biological effect for different compounds.

Structural formula for the products	Solvents	Biological effect	Radius of the inhibitor activity area
	Cyclohexanone	++	15 mm
	Cyclohexanone	+++	32 mm

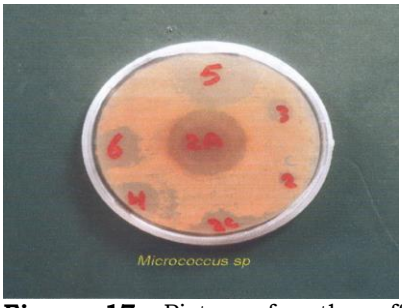


Figure 17: Picture for the effect of different compounds on bacteria, *Micrococcus sp.*
For bacteria, *Escherichia* the radius of the inhibitor activity areas were between 11-28 mm

Table 6: Biological effect for different compounds.

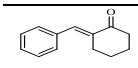
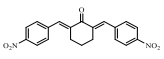
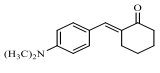
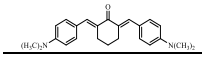
Structural formula for the products	Solvents	Biological effect	Radius of the inhibitor activity area
	Cyclohexanone	++	17 mm
	Cyclohexanone	+++	20 mm
	Cyclohexanone	+++	25 mm
	Cyclohexanone	+++	28 mm

Figure 18: Picture for the effect of different compounds on bacteria, *Escherichia.*

As a result of the computation study, we realized that (*E)-2-benzylidenecyclohexan-1-one*, is less in energy bending and more stable, followed by the compound 2,6-bis ((E)-4-(dimethylamino) benzylidene) cyclohexan-1-one and finally the compound 2,6-di ((E)- benzylidene) cyclohexan-1-one has the highest energy and less stable. Regarding to this result the compound 2, 6 - di ((E)-benzylidene) cyclohexan-1-one, has high biological activity Figure 18.

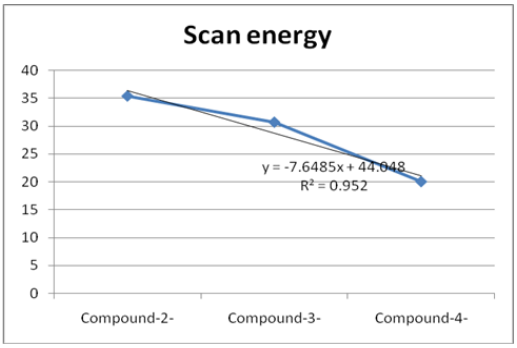


Figure 19: Energy bending

The ratio of activity for the different compounds Figure 18.

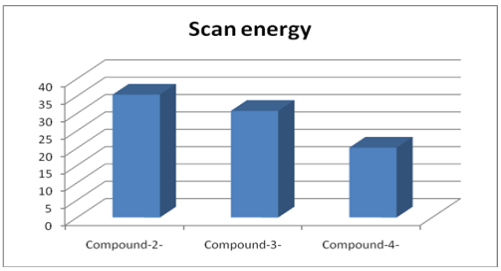


Figure 20: Ratio of activity.

4. Conclusion

The study concluded that the computational study for synthesised derivatives of mono- and diarylidine cyclohexanone was in agreement with the results of the biological activity of these compounds.

References

[1]- David C. Young, Computational Chemistry: *A Practical Guide for Applying Techniques to Real-World Problems, New York* **2001**, 408.

[2]- M. F. Schlecht, Molecular Modeling on the PC. *Wiley-VCH, New York* **1998**, 3-10.

[3]- Aileen H., Roger R., Timothy O., ACS Chem. Neurosci. **2011**, 2, 402–410

[4]- Arixan S. Z., Suschitzky H., *Org. Chem.* , **1961,** 10, 2242, 426.

[5]- Kohler and Chadwell, *Org. Syn.*, **1922**, 2, 1.

[6]- Morrison and Boyed, *Org. Chem.*, 3th edition, p. 709-711, Allyn & Bacon, Inc. **1977**.

[7]- Sammour A., Marei A. and Hussein M.H.M, *J. Chem. U.A.R*, 12(4), 451, **1969**.

[8]- Nakano, T., Irifune, S., Umano, S., Inada, A., Ishii, Y. and Ogawa, M. *J. Org. Chem.*, **1987**, 52, 2239-2244.

[9]- Li, J.T., Yang, W.Z., Chen, G.F. and Li, T.S. *Syn. Comm.*, **2003**, 33, 2619-2625.

[10]- Yadav, J.S., Reddy, B.V.S., Nagaraju, A. and Sarma, J.A.R.P. Microwave Assisted Synthesis of α,α'-Bis(benzylidene) ketones in Dry Media. *Syn. Comm.*, **2002**, 32, 893-896.

[11]- Zhang, X.Y., Fan, X.S., Niu, H.Y. and Wang, J.J. *Green Chemistry*, **2003**, 5, 267-269.

[12]- Wang, L., Sheng, J., Tian, H., Han, J., Fan, Z. and Qian, C. *Syn.*, **2004**, 3060-3064.

[13]- Bigdeli, M.A., Mahdavinia, G.H., Jafari, S. and Hazarkhani, H. *Cat. Comm.*, **2007**, 8, 2229-2231.

[14]- Morrison and Boyed, *Org. Chem.*, 6th edition, p. 979, Prentice Hall International, Inc., New Jersey **1992**.

[15]- Finkbeiner H., Amer J., *J. Am. Chem. Soc.*, **1956**, 87, 4588.

[16]- Glaisen L., Claparede A., *Chem. Berichte*, **1881**, 14, 2460.

[17]- P. W. Atkins, and R. S. Friedman, *Mol. Quan. Mech.*, Oxford, **1997**, 76, 2, 170.

[18]- M.Vieth, J. D.Hirst, B. N. Domini, H. Daigler, and C. L. Brooks, *J. Comp. Chem.*, **1998**, 19, 1612–1622.

[19]- Schmidt J., *Chem. Berichte*, **1881**, 14, 1459.

[20]- Singh, N., Pandey, J., Yadav, A., Chaturvedi, V., Bhatnagar, Sh., Gaikwad, A.N., Sinha, S.K., Kumar, A., Shukla, P.K. and Tripathi, R.P. *Eu. J. Med. Chem.*, **2009**, 44, 1705-1709.

[21]- Mahdavinia, G.H. and Mirzazadeh, M. *E-J. Chem.*, **2012**, 9, 49-54.

[22]- Rahman, A.F.M.M., Ali, R., Jahng, Y. and Kadi, A.A. *Mol.*, **2012**, 17, 571-583.

[23]- Huang H., Jan S., Uckun F., *Tet. Lett.* **2000,** 41, 1699-1702.

[24]- Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.;Montgomery, J.A.; Vreven, T., Jr.; Kudin, K.N.; Burant, J.C.; *et al. Gaussian 03, Revision B.03*; Gaussian, Inc.: Pittsburgh, PA, USA, **2003**.

[25]- Aizenshtar, Hausmann M., Blum J., *J. My. Chem.*, **1977**, 42.