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Full Length Research Paper

Design, synthesis and bioassay of novel coumarins

Redha I. Al-Bayati[1], Ahmed A. Hussain Al-Amiery[2]* and Yasmien K. Al-Majedy[2]

[1]Chemistry Department, College of Science, Al-Mustansiriyah University, Baghdad, Iraq.
[2]Biochemical Division, Department of Applied Science, University of Technology, Baghdad, Iraq.

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In Iraq like most third world countries, attempts to discover new antibiotic drugs derived from coumarins moreover develop the branch of applied in organic chemistry. Novel coumarin derivatives were synthesized in a good yield through converting lacton to lactam and study the biological activity of the synthesized compounds. Coumarins were characterized by elemental analysis, FT-IR, ^{1}H-NMR and UV/visible spectra. The novel coumarins have been tested *in vitro* against (gram positive bacteria *Staphylococcus aureus* and against other gram negative bacteria, such as *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Proteus vulgaris*; in order to assess their antimicrobial properties. Moreover, charge, bond length, bond angle, twist angle, heat of formation and steric energy were calculated by using of the ChemOffice program. The study indicates that these coumarins have high activity against tested bacteria. Based on the reported results, it may be concluded that the coumarin act as synthons for synthesis of new coumarin derivatives through the replacement of oxygen atom by nitrogen atom.

Key words: Biological activity, coumarins, oxoquinolin, thiourea.

INTRODUCTION

Coumarins owe their class name to 'coumarou', the vernacular name of the tonka bean, from which coumarin itself was isolated in 1820 (Bruneto, 1999). Coumarins belong to a group compounds known as the benzopyrones, all of which consist of a benzene ring joined to a pyrone. Coumarin and the other members of the coumarin family are benzo-α-pyrones, while the other main members of the benzopyrone group contain the pyrone group (Keating and O'Kennedy, 1997). Coumarins may also be found in nature in combination with sugars, as glycosides. The coumarins can be roughly categorized as the following (Murray et al., 1982):

- Simple: these are the hydroxylated, alkoxylated and alkylated derivatives of the parent compound, coumarin, along with their glycosides.
- Furanocoumarins: these compounds consist of a five-membered furan ring attached to the coumarin nucleus, divided to linear and angular types with substituents at one or both of the remaining benzenoid positions.
- Pyranocoumarins: members of this group are analogous to the furanocoumarins, but contain a six-membered ring.
- Coumarins substituted in the pyrone ring.

Coumarins have a variety of bioactivities including anticoagulant, estrogenic, dermal photosensitizing, antimicrobial, vasodilator, molluscacidal, antithelmintic, sedative and hypnotic, analgesic and hypothermic activity (Soine, 1964; O'kennedy and Thornes, 1997; Czerpack, 1982; Jund et al., 1971; El-Ansary et al., 1992; Reddy and Somayajulu, 1981; Abd Allah, 2000; Wenner, 1953; Parmer and Kumar, 1968; Bhamaria, 1968; Abdel-Al et al., 1983; Gupta et al., 1979; Mansour et al., 2003; Dutta et al., 1986). Controversy about the activity of the coumarins as anti-inflammatory agents exists, since some authors have already reported that coumarins do not exert potent activity in conventional short-term tests (Hoult and Paya, 1996). A valuable method for the synthesis of coumarins is the Pechmann reaction, of

*Corresponding author. E-mail: dr.ahmed1975@gmail.com.

Table 1. The physical properties for the coumarins (1-20).

No.	Name	Melting points ℃	Yield %
1	2H-chromen-2-one	70-73	85
2	6-nitro-2H-chromen-2-one	140-142	70
3	1-aminoquinolin-2(1H)-one	130-132	55
4	1-amino-6-nitroquinolin-2(1H)-one	165-168	65
5	1-(2-oxoquinolin-1(2H)-yl)thiourea	69-73	55
6	[1,2,4]triazolo[1,5-a]quinoline-2-thiol	165-168	35
7	1-(4,6-dimethyl-2-thioxopyrimidin-1(2H)-yl)quinolin-2(1H)-one	Oily	-
8	1-(6-methyl-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)quinolin-2(1H)-one	Oily	-
9	5-allyl-3-(2-oxoquinolin-1(2H)-yl)-2-thioxo-dihydropyrimidine-4,6(1H,5H)-dione	148-150	80
10	1-(4-hydrazono-6-methyl-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)quinolin-2(1H)-one	Oily	-
11	1-(4-(benzylidenehydrazono)-6-methyl-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)quinolin-2(1H)-one	160-164	80
12	1-(4-hydroxybenzylideneamino)quinolin-2(1H)-one	218-221	80
13	1-(4-chlorobenzylideneamino)quinolin-2(1H)-one	199-202	80
14	1-(4-hydroxybenzylideneamino)-6-nitroquinolin-2(1H)-one	189-192	80
15	1-(4-chlorobenzylideneamino)-6-nitroquinolin-2(1H)-one	185-189	80
16	(Z)-3-((E)-6-methyl-1-(2-oxoquinolin-1(2H)-yl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-ylideneamino)-2-phenyl-2,3-dihydro-1,3-oxazepine-4,7-dione	170-174	30
17	(Z)-3-(4-hydroxyphenyl)-2-(2-oxoquinolin-1(2H)-yl)-2,3-dihydro-1,2-oxazepine-4,7-dione	191-194	30
18	(Z)-3-(4-chlorophenyl)-2-(2-oxoquinolin-1(2H)-yl)-2,3-dihydro-1,2-oxazepine-4,7-dione	180-184	35
19	(Z)-3-(4-hydroxyphenyl)-2-(6-nitro-2-oxoquinolin-1(2H)-yl)-2,3-dihydro-1,2-oxazepine-4,7-dione	185-188	35
20	(Z)-3-(4-chlorophenyl)-2-(6-nitro-2-oxoquinolin-1(2H)-yl)-2,3-dihydro-1,2-oxazepine-4,7-dione	79-183	35

phenols, using concentrated sulfuric acid as the catalyst. By-products are formed and the reaction needs a long time and introduces corrosion problems. For these reasons there have been some attempts to find alternative environmentally benign synthetic routes.

Some organic acids and metallic Lewis acids are also examined in this transformation (Gunnewegh et al., 1995). Although these methods are suitable for certain synthetic applications, many of these procedures are associated with one (or more) disadvantages such as expensive or corrosive reagents, long reaction time, tedious workup and low selectivity. Large amounts of solid supports result in the generation of a large amount of toxic waste. Pechmann reactions have also been conducted in chloroaluminate ionic liquids (Benyaram et al., 2001).

MATERIALS AND METHODS

All chemical used were of reagent grade (supplied by either Merck or Fluka) and used as supplied. The FTIR spectra in the range (4000 – 600) cm^{-1} were recorded as KBr disc on FTIR 8300 Shimadzu spectrophotometer.

The UV-Visible spectra were measured using Shimadzu UV-Vis. 160 A spectrophotometer in the range (200 - 1000) nm. Proton NMR spectra were recorded on Bruker -DPX 300 MHz spectrometer with TMS as internal standard in Jordan University. ^{13}C-NMR was recorded on Bruker 400 MHz spectrophotometer using TMS as internal standard. Elemental micro analysis was carried out using C.H.N elemental analyzer model 5500-Carlo Erba instrument (Italy). Gallen Kamp M.F.B.600.010 F melting point apparatus were used to measure the melting point of all the prepared compounds.

Synthesis of coumarin (1)

Coumarin was synthesized chemically by the reaction of phenol (4.7 g, 0.05 mole) and (5.8 g, 0.05 mole) of malic acid in 5 mL. concentrated sulfuric acid at 120-130°C according to the literature method (Al-Amiery , 2007; Habib, 2006). Melting point and yield are listed in Table 1.

Synthesis of nitrocoumarin (2)

A mixture of coumarin (0.02 mole) and concentration sulfuric acid (10 mL) was stirred at 0℃ for 15 min. Then a mixture of concentration nitric acid (0.092 mole) and sulfuric acid (0.087mole) was added. The temperature was kept at 0 - 5℃ during the period of addition the mixture was continuously stirred for one hour at 5℃. The reaction mixture was poured on to ice, the precipitate was filtered and dried then purified by column chromatography using silica gel eluting with petroleum ether/ benzene (1:1) (A-Amiery Hussain, 2007; Habib, 2006). Melting point and yield are listed in Table 1.

Synthesis of 1-aminoquinolin-2(1H)-one and 1-amino-6-nitroquinolin-2(1H)-one (3-4)

Solution of (0.035 mole) coumarin (or Nitrocoumarin) and hydrazine (0.07mole) in absolute ethanol was refluxed for 24 h, the solvent was concentrated and the separated solid product was filtered and washed with cold ethanol (A-Amiery Hussain, 2007; Habib, 2006) and recrystallized from ethanol-water.

1-aminoquinolin-2(1H)-one (3)

Elemental analysis found %; C, 67.02; H, 4.45; N, 16.92. Proton NMR (4.2 s, for NH_2, m, 6.2(1H) for H-olifinic, m, 7.4(H) for H-aromatic. ^{13}C-NMR: 126,127,127.8,128,123.3,128.5,129,155,157 .

1-amino-6-nitroquinolin-2(1H)-one (4)

Elemental analysis found %; C, 51.77; H, 3.02; N, 19.98. Proton NMR (1.4 m for NH_2, d. 6.5(1H) for H-olifinic, dd. 7.2(1H) for H-olifinic, m. 7.5(H) for H-aromatic, m. 7.9(H) for H-aromatic. Melting points andyield are listed in Table 1.

Synthesis of 1-(2-oxoquinolin-1(2H)-yl)thiourea (5)

A mixture of coumarin (5.8 g, 0.04 mole) with thiosemicarbazide (3.6 g, 0.04 mole) in dry benzene (40 mL) was refluxed for 8 h removing solvent by reducing pressure then recrystallized from chloroform. Melting points and yield are listed in Table 1.

Synthesis of [1,2,4]triazolo[1,5-a]quinoline-2(1H)-thione (6)

2.3 g, 0.01 mole of 1-(2-oxoquinolin-1(2H)-yl) thiourea in 1.4 g, 0.01 mole K_2CO_3 in 200 mL. H_2O was refluxed for (6 h) then left to cool in ice -water. The solid was filtered, washed with 2%HCl then water and recrystallized twice from dioxane. (A-Amiery and Hussain, 2007; Habib, 2006). Elemental analysis found %; C, 58.88; H, 3.12; N, 19.76. Proton NMR (1.2 m for NH, d. 5.4(1H) for H-olifinic, d. 6.6(1H) for H-olifinic, 7.1(1H) for H-aromatic, 7.5(1H) for H-aromatic. Melting points andyield are listed in Table 1.

Cyclization with dioxocompounds (7-9)

Dioxocompouds (acac or eaa or) (0.002 mole) were added to (0.002 mole) 1-(2-oxoquinolin-1(2H)-yl) thiourea in 30 ml ethanol and refluxed for (7 - 8 h), then left to cool. The precipitate was filtered, then recrystallized from ethanol. Melting points and yield are listed in Table (1).

Reaction of 1-(6-methyl-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)quinolin-2(1H)-one (8) with hydrazine (10)

Reflux of the 0.01 mole compound (8) with 0.01 mole of hydrazine for 6 h in ethanol. Melting points and yield are listed in Table (1).

Schiff base formation (11-15)

A mixture of 0.01 mole of 1-(4-hydrazono-6-methyl-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)quinolin-2(1H)-one **(10)** and 0.0l mole of aldehyde or ketone in (10 ml) absolute ethanol was refluxed in water bath for (2 h.) then left to cool in ice -water. The solid was filtered, washed with 2%HCl then water and recrystallized twice from ethanol. Melting points and yield are listed in Table (1).

Reaction of Schiff base with maleic anhydride (16-20)

Mixture of 0.01 mole of Schiff base with 0.01 mole of maleic anhydride in 10 mL of dry benzene was refluxed in water bath for 2 h. The solvent was removed and the precipitate was recrystallized from tetrahydrofuran (THF) (A-Amiery, 2007). Melting points and yield are listed in Table 1.

Hole diffusion method (Antimicrobial action)

Hole diffusion method was used to measure the inhibitory activity as indicated by the diameter of the inhibition zone, for each concentration, 100 µL of the coumarins (2 - 20), (Dissolved in DMSO) were placed in 5 mm diameter wells on nutrient agar inoculated spontaneously with the pathogens to be tested against. The plates were incubated at 37°C for 48 h. The clear zone around the wells was measured as inhibition zones. The absence of a clear zone around the well was taken as inactivity.

RESULTS AND DISCUSSION

Synthesis of coumarin (1)

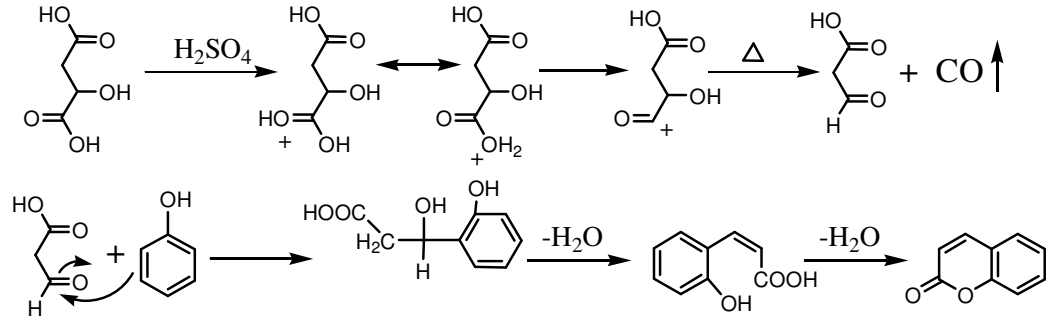
Coumarins are the key intermediates for the compounds synthesized later in this work. Coumarins has been prepared by the Pechmann condensation by reaction of phenol with malic acid using concentrated sulfuric acid as condensing agent with stirring at (120-130C˚), as outlined in Scheme 1. FT-IR (3100 cm^{-1} for C-H aromatic, 1720 cm^{-1} for carbonyl group, 1575 cm^{-1} for C=C and 1150 cm^{-1} for lacton). UV-visible spectroscopy (310 nm for C = C - C = O, 290 and 260 nm). We can use Perkin reaction to prepare coumarin but the yield of coumarin is generally low. The reaction mechanism involves denaturation of malic acid by concentrated sulfuric acid with loosing H_2O and CO and transferring to formylacetic acid that represents 1,3–dicarbonyl compound (Scheme 1). There is another mechanism (Scheme 2) different from the previous mechanism in the end because of the formation of phenoxide ion.

The difference in the reactivity of the carbon atoms in the coumarin molecules toward electrophilic substitution was observed. This is indicated by the (-ve) charge on the different carbons of coumarin. The data obtained for the minimized geometry that is, charge, bond length, bond angle, twist angle, heat of formation and steric energy of the reactants, intermediate and the products were calculated using semi empirical AMI module in the CS Chemoffice molecular modeling package (ChemDraw Ultra 9.0). The data obtained show that the heat of formation is about (-30.42 Kcal) and the highest atomic charge in coumarin molecule is at [C (3) (-0.232)] the next charge value is at [C (6) (-0.16)] and [C (8) (-0.14)] (Table 3).

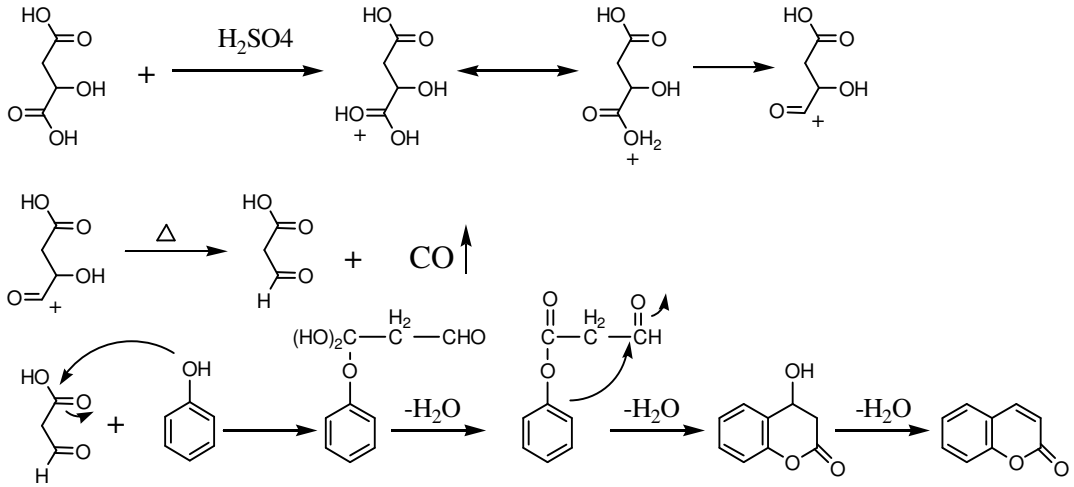
These data show clearly that these three carbon atoms are the most reactive toward the electrophilic substitution reaction, in coumarin. The determined bond angle (Table 2) and twist angle and 3D-geometrical structure (Figure 1), indicate that this molecule is planar.

Synthesis of nitrocoumarin (2)

The orientation of nitration of coumarin molecule is greatly affected by the substituent's that may alter the reactivity of carbon atoms toward the electrophilic substitution reaction. The data obtained from the theoretical



Scheme 1. The mechanism of coumarin formation.



Scheme 2. The mechanism of coumarin formation.

Table 2. The theoretical measurements of coumarin.

S/N	Atom	Bond atom	Bond length	Angle atom	Angle	Dihedral atom	Angle
2	C	-	-	-	-	-	-
4	C	C(2)	1.3510	-	-	-	-
5	C	C(4)	1.3370	C(2)	117.5999	-	-
12	H	C(4)	1.1000	C(2)	121.6929	C(5)	120.7072
6	C	C(5)	1.3370	C(4)	120.0003	C(2)	0.0000
13	H	C(5)	1.1000	C(4)	119.9997	C(6)	120.0000
7	C	C(6)	1.3370	C(5)	119.9988	C(4)	-179.4299
11	C	C(6)	1.3370	C(5)	119.9999	C(7)	119.9989
1	O	C(11)	1.3550	C(6)	124.2999	C(5)	0.0000
10	C	C(11)	1.3370	O(1)	115.6991	C(6)	119.9990
8	C	C(7)	1.3370	C(6)	119.9997	C(5)	-179.9874
14	H	C(7)	1.1000	C(6)	120.0000	C(8)	120.0003
9	C	C(10)	1.3370	C(11)	119.9999	O(1)	-179.9862
15	H	C(8)	1.1000	C(7)	119.9954	C(9)	120.0103
16	H	C(9)	1.1000	C(8)	120.0107	C(10)	119.9956
17	H	C(10)	1.1000	C(9)	119.9999	C(11)	120.0002
3	O	C(2)	1.2080	O(1)	117.6851	C(4)	116.5435

Table 3. Atomic charge of coumarin molecule.

Atom	Charge	Atom	Charge	Atom	Charge
[O(1)]	O 0.002	[C(7)]	C -0.023	[H(13)]	H 0.022
[C(2)]	C 0.544	[C(8)]	C -0.072	[H(14)]	H 0.023
[O(3)]	O -0.699	[C(9)]	C -0.013	[H(15)]	H 0.026
[C(4)]	C -0.122	[C(10)]	C -0.096	[H(16)]	H 0.025
[C(5)]	C 0.064	[C(11)]	C 0.272	[H(17)]	H 0.029
[C(6)]	C -0.015	[H(12)]	H 0.034	-	-

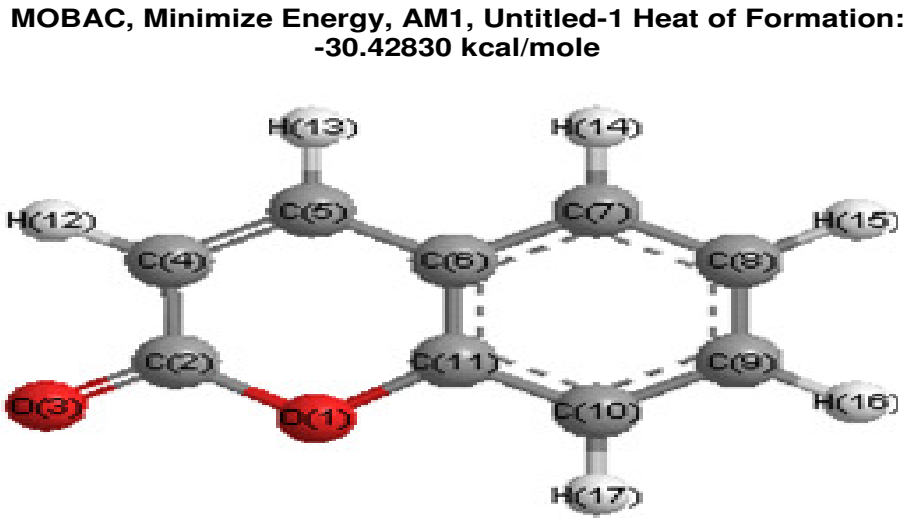


Figure 1. 3D-geometrical structure of coumarin molecule.

Table 4. The theoretical measurements of nitrocoumarin.

S/N	Atom	Bond atom	Bond length	Angle atom	Angle	Dihedral atom	Angle
2	C	-	-	-	-	-	-
4	C	C(2)	1.3510	-	-	-	-
5	C	C(4)	1.3370	C(2)	117.6001	-	-
15	H	C(4)	1.1000	C(2)	121.6926	C(5)	120.7073
6	C	C(5)	1.3370	C(4)	120.0002	C(2)	0.0000
16	H	C(5)	1.1000	C(4)	119.9999	C(6)	119.9998
7	C	C(6)	1.3370	C(5)	119.9989	C(4)	-179.4299
11	C	C(6)	1.3370	C(5)	119.9998	C(7)	119.9988
1	O	C(11)	1.3550	C(6)	124.2998	C(5)	0.0000
10	C	C(11)	1.3370	O(1)	115.6991	C(6)	119.9991
8	C	C(7)	1.3370	C(6)	119.9997	C(5)	-179.9874
17	H	C(7)	1.1000	C(6)	120.0001	C(8)	120.0002
9	C	C(10)	1.3370	C(11)	119.9997	O(1)	-179.9862
12	N	C(8)	1.3000	C(7)	119.9956	C(9)	120.0101
18	H	C(9)	1.1000	C(8)	120.0108	C(10)	119.9955
19	H	C(10)	1.1000	C(9)	120.0001	C(11)	120.0002
3	O	C(2)	1.2080	O(1)	117.6851	C(4)	116.5433
13	O	N(12)	1.1318	C(8)	112.5720	C(7)	-180.0000
14	O	N(12)	1.3160	C(8)	127.4279	O(13)	120.0001

calculation from the minimized geometry of coumarin (Figure 2), show that charges at the C (3) atom is (-0.2322). The theoretical calculation shows that the steric energy, for introducing (NO_2) group at C (3) is relatively higher (about (51.688 kcal/mole) with respect to that for the other carbons. The theoretical calculation data for the minimized geometry of unsubstituted coumarin shows that the charges at C(6) and C(8) are (- 0.1605 and -0.1122) respectively as in structure below (Tables 4 and 5). Therefore it is expected that the electrophilic substitution occurs at C (6). The final heat of formation of 6-nitrocoumarin is (-25.55 kcal) and 8-nitrocoumarin is (-20.618 kcal). According to the summation of the effects of atomic charge and the final heat of formation and the steric energy of the corresponding nitration from these data it could be suggested that the substitution occurred at C (6). Nitro coumarin is prepared by treatment of coumarin with a mixture of concentrated sulfuric acid and concentrated nitric acid at (0 - 5℃). The nitration reaction depends on the oxygen of pyron ring toward ortho or para and R group. The IR spectral data show C=C aromatic stretching frequency was (1580 cm^{-1}). Generally these frequencies are sensitive to the type and position of the substituent, other significant bands were observed at (1720 cm^{-1}) being assigned to the C=O stretching frequency and significant band were observed about (1350 and 1520 cm^{-1}) being assigned to the NO_2 stretching frequency. UV-visible spectroscopy 320.0 nm.

Synthesis of the coumarins (3-5)

Coumarin was converted to the compounds (3 - 5) by it reaction with hydrazine hydrate or thiosemicarbazide, (Table 6). The quinolone derivatives are important biologically active compounds and synthons in organic synthesis due to the introduction of several drug-receptor binding models, which enable systematic and rational design of novel inhibitor of various enzymes. The nucleophilic reaction of coumarin with hydrazine hydrate or thiosemicarbazide may proceed through ring opening of pyrano ring, Scheme 3.

The data obtained for minimizing geometry for compounds (3 - 5) show that C (9) and C (11) have positive charge in the molecule make the nucleophile (NH_2-) attack these carbons. Then there are two possible of (NH_2-) attacks as shown in Scheme 4. The determined bond angle, (Tables 7 - 8) twists angle and 3D-geometrical structure (Figure 3) for compounds (3-5), indicate that these molecules are planar.

Synthesis of [1,2,4]triazolo[1,5-a]quinoline-2(1H)-thione (6)

FT-IR (disappearance of NH_2 and appear of 2400 cm^{-1} for S-H, 1620 cm^{-1} for C=N, 3200 cm^{-1} for N-H and1310 cm^{-1} for C=S). UV-visible spectroscopy (320, 270 and 230 nm). The determined bond angle and twist angle and 3D-geometrical structure for compound (6), indicate that this molecule is planar (Scheme 5).

Cyclization with dioxocompounds (7-9)

Compounds (7-9) were obtained by thermal cyclization of (5) with acetylacetone (7), ethylacetoacetate (8) and ethyl allylmalonate (9). U.V. spectra of these coumarins (7-9) have been measured in ethanol and show three absorption bands, Table 9.

Synthesis of compounds 7-9

These compounds were synthesized by cyclization of the derivative of thiosemicarbazide with dioxo compounds as shown in schemes 6 - 8.

Synthesis of Schiff base

Schiff bases are prepared by condensation of aromatic aldehydes and aromatic primary amines, identified by their Uv-visible and IR spectra andused immediately in the reactions to follow as shown in scheme 9:

Reaction of Schiff base with maleic anhydride [16-20]

Treatment of Schiff bases with maleic anhydride results in the formation of (Z)-3-((E)-6-methyl-1-(2-oxoquinolin-1(2H)-yl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-ylideneamino)-2-phenyl-2,3-dihydro-1,3-oxazepine-4,7-dione, Table 10, as shown in scheme 10.

Antibacterial activity

The antimicrobial screening data show that the compounds exhibit antimicrobial properties and it is important to note that the novel coumarins exhibit more inhibitory effects than the coumarin molecule. From Figures 4 - 11 it is clear that the zone of inhibition is much larger against the gram-negative bacteria (*E. coli*) and gram positive bacteria (*S. aureus*). The increased activity of the novel coumarins can be explained by the azomethane group and that act as more powerful and potent bactericidal agents, thus killing more of the bacteria than the coumarin molecule. The π-electron delocalization over the coumarins increases the lipophilic character and favours its permeation through the lipoid layer of the bacterial memberanes.

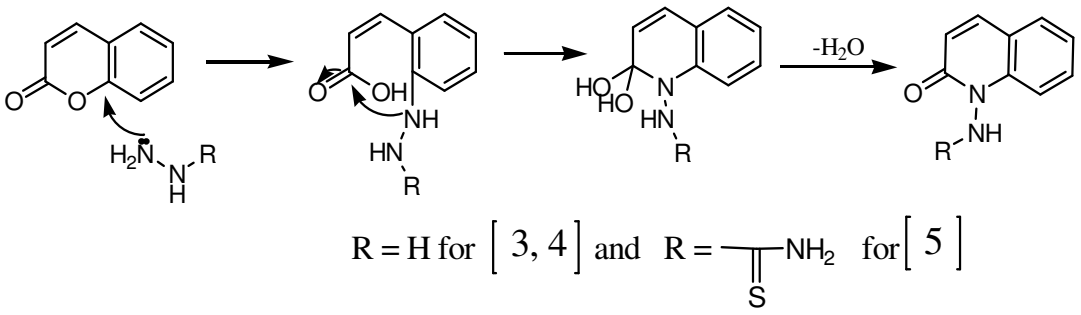
It was concluded that coumarins acting as electrophilic agents have a positive effect and inhibited bacterial growth (Elinos-Báez et al., 2005; Duncana et al., 2006).

Table 5. Atomic charge of nitrocoumarin molecule.

Atom	Charge	Atom	Charge	Atom	Charge
[O(1)]	O -0.000	[C(8)]	C 0.063	[H(15)]	H 0.029
[C(2)]	C 0.542	[C(9)]	C 0.006	[H(16)]	H 0.012
[O(3)]	O -0.733	[C(10)]	C -0.086	[H(17)]	H 0.012
[C(4)]	C -0.128	[C(11)]	C 0.306	[H(18)]	H 0.019
[C(5)]	C 0.095	[N(12)]	N 1.236	[H(19)]	H 0.024
[C(6)]	C -0.003	[O(13)]	O -0.505		
[C(7)]	C 0.012	[O(14)]	O -0.898		

Table 6. The UV-visible and IR spectroscopy for the coumarins [3-5].

No.	Uv-visible (λ_{max} nm)	IR spectroscopy (cm^{-1})				
		NH_2	N-H	C=O	C=S	C-N
1	325	3190	-	1660	-	1301
2	300	3201	-	1705	-	1334
3	331	3300-3450	3200	1620	1320	1324



Scheme 3. The reaction of n-aminocoumarin formation.

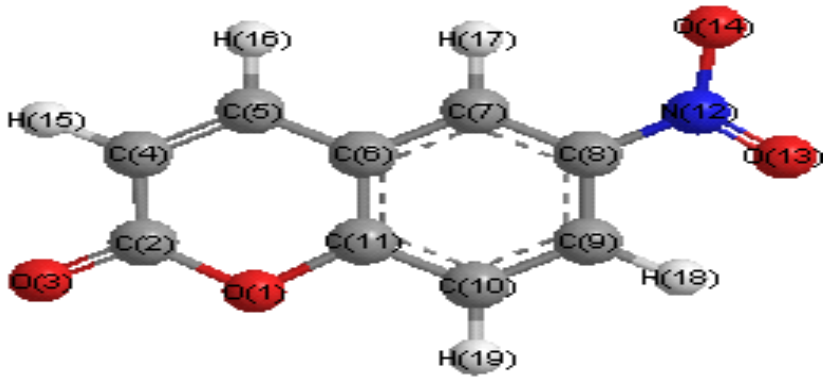
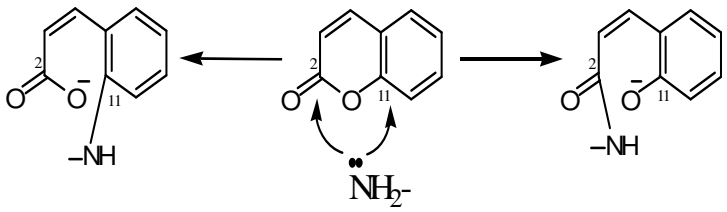


Figure 2. 3D-geometrical structure of 6-nitrocoumarin molecule. MOPAC, Minimize Energy, AM1, Untitled-1 Heat of Formation: -25.55416 kcal/mole.



Scheme 4. The two possible attacks of NH_2.

Table 7. The theoretical measurements of compound 3.

S/N	Atom	Bond atom	Bond length	Angle atom	Angle	Dihedral atom	Angle
4	C	C(2)	1.4637				
5	C	C(4)	1.3478	C(2)	121.3134		
13	H	C(4)	1.0997	C(2)	115.0842	C(5)	123.6022
6	C	C(5)	1.4395	C(4)	120.6763	C(2)	-0.0748
14	H	C(5)	1.1023	C(4)	121.4648	C(6)	117.8588
7	C	C(6)	1.4074	C(5)	120.4482	C(4)	179.6378
11	C	C(6)	1.4231	C(5)	119.7607	C(7)	119.7911
1	N	C(11)	1.4129	C(6)	119.5979	C(5)	-0.3980
10	C	C(11)	1.4217	N(1)	122.0493	C(6)	118.3526
8	C	C(7)	1.3819	C(6)	120.9171	C(5)	-179.8376
15	H	C(7)	1.1012	C(6)	118.7020	C(8)	120.3810
9	C	C(10)	1.3827	C(11)	120.3240	N(1)	-179.7272
16	H	C(8)	1.0993	C(7)	120.5565	C(9)	119.9147
17	H	C(9)	1.1012	C(8)	119.4166	C(10)	119.4970
18	H	C(10)	1.1013	C(9)	119.0951	C(11)	120.5807
12	N	N(1)	1.3751	C(2)	120.9227	C(11)	118.4088
3	O	C(2)	1.2482	N(1)	118.4892	C(4)	123.5253
19	H	N(12)	1.0161	N(1)	107.9225	C(2)	54.9353
20	H	N(12)	1.0160	N(1)	107.7873	H(19)	106.4796

Table 8. Atomic charge of compound 3.

Atom	Charge	Atom	Charge	Atom	Charge
[N(1)]	N 0.635	[C(8)]	C -0.080	[H(15)]	H 0.023
[C(2)]	C 0.314	[C(9)]	C -0.029	[H(16)]	H 0.025
[O(3)]	O -0.857	[C(10)]	C -0.089	[H(17)]	H 0.025
[C(4)]	C -0.118	[C(11)]	C 0.108	[H(18)]	H 0.027
[C(5)]	C -0.027	[N(12)]	N -0.211	[H(19)]	H 0.124
[C(6)]	C -0.012	[H(13)]	H 0.029	[H(20)]	H 0.124
[C(7)]	C -0.031	[H(14)]	H 0.022		

Table 9. The Uv-visible and IR spectroscopy for the coumarins [7-9].

No.	Uv-visible (λ_{max} nm)	IR spectroscopy (cm^{-1})					
		C-H *Aromatic*	C=C *Aromatic*	C=O	C=N	C-S	N-H
7	305	3021	1550	1687	1625	1215	-
8	330	3032	1555	1700, 1655	-	1220	3270
9	305	3045	1600	1695	-	1255	3301

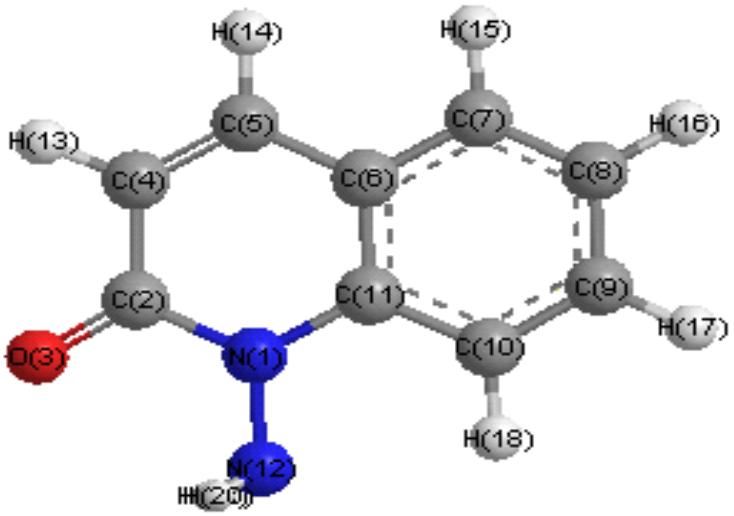
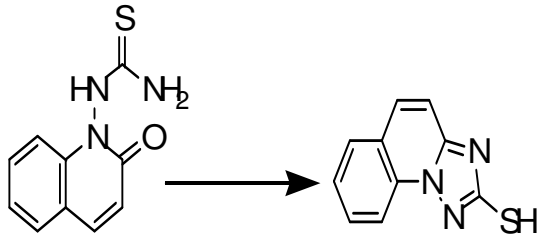
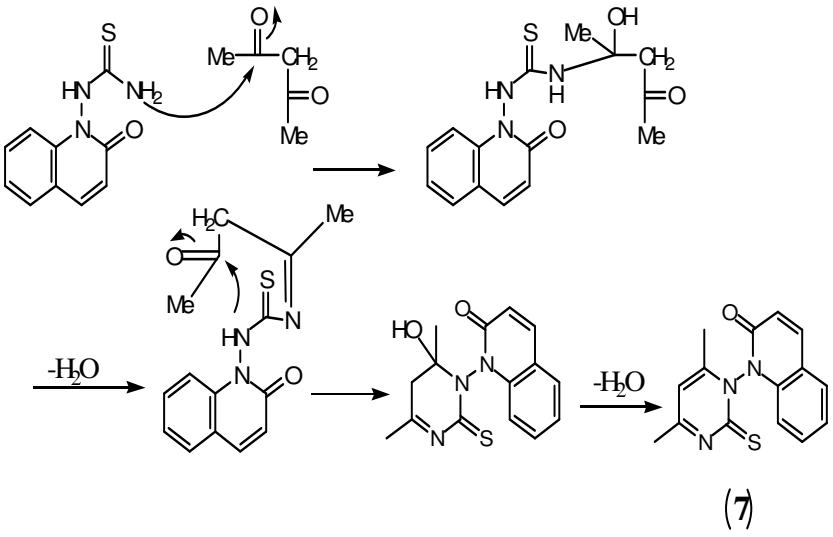


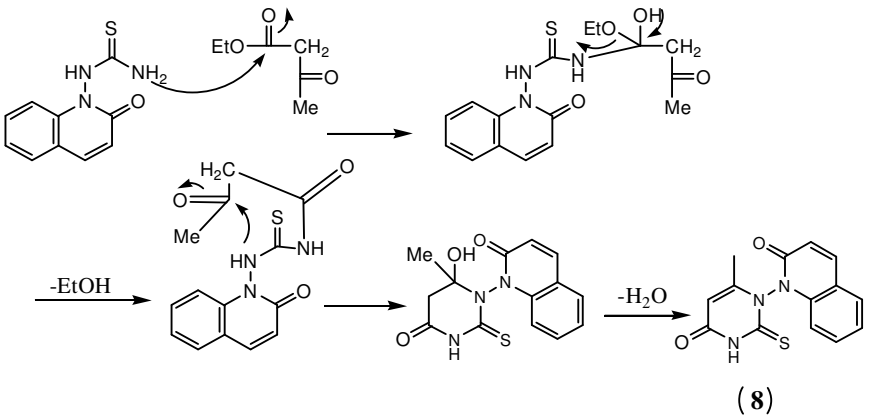
Figure 3. 3D-geometrical structure of compound 3. MOPAC, Minimize Energy, AM1, Untitled-1 Heat of Formation: 36.05615 kcal/mole.



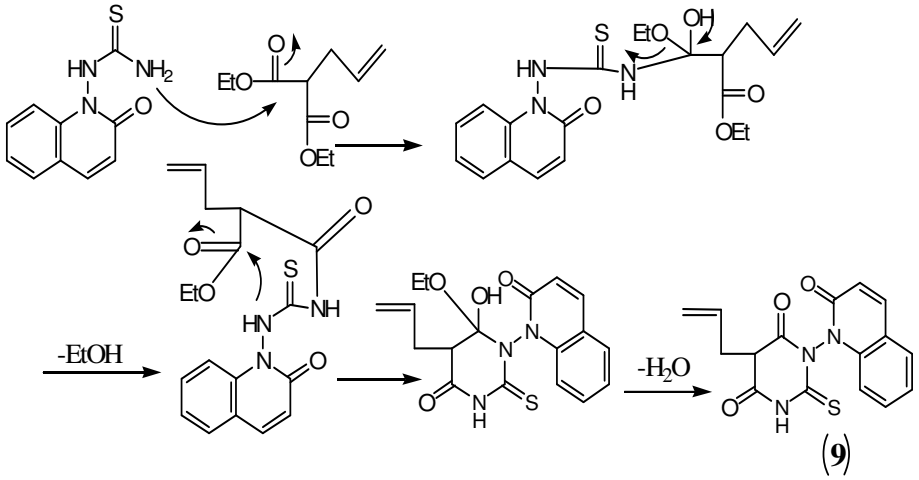
Scheme 5. The synthesis of compound 6.



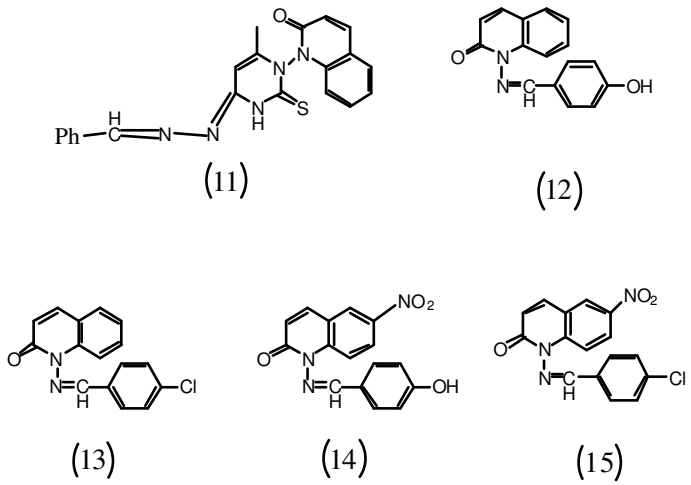
Scheme 6. The reaction mechanism of the formation of the compound (7).



Scheme 7. The reaction mechanism of the formation of the compound (8).



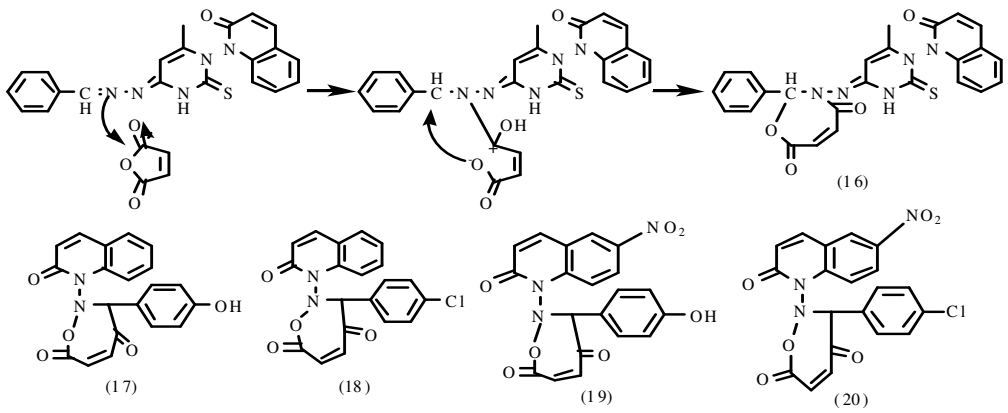
Scheme 8. The reaction mechanism of the formation of the compound (9).



Scheme 9. Synthesis of Schiff base 11-15.

Table 10. The UV-visible and IR spectroscopy for the coumarins (10-20).

No.	Uv-visible (λ_{max} nm)	IR spectroscopy (cm^{-1})					
		C=C	C-N	C=O	C-O	N-H	Others
[10]	305	1602	1305	1696	1125	3375-3398	C-S,1221
[11]	285	1595	1300	1701	1200	3290	C-S, 1230
[12]	280	1600	1285	1960	1165	-	O-H, 3375
[13]	300	1590	1290	1690	1145	-	C-Cl 726
[14]	270	1580	1289	1865	1115	-	O-H, 3290; NO_2,1432-1530
[15]	265	1575	1295	1700	1125	-	C-Cl, 730; NO_2,1435-1520
[16]	310	1600	1320	1703	1171	3345	C-S,1265
[17]	300	1600	1290	1670	1165	-	O-H, 3370
[18]	324	1570	1315	1698	1150	-	C-Cl, 720
[19]	315	1560	1285	1655	1155	-	O-H, 33310; NO_2,1430-1615
[20]	320	1590	1290	1690	1155	-	C-Cl, 734; NO_2,1440-1540



Scheme 10. Cyclization of Schiff base by using of maleic anhydride (16-20).

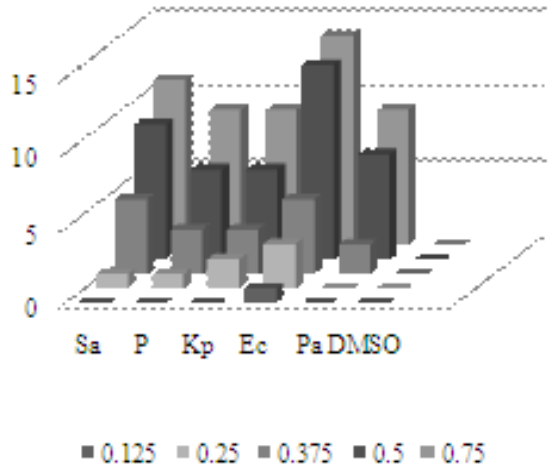


Figure 4. The antibacterial activity of coumarins (Abd Allah, 2000).

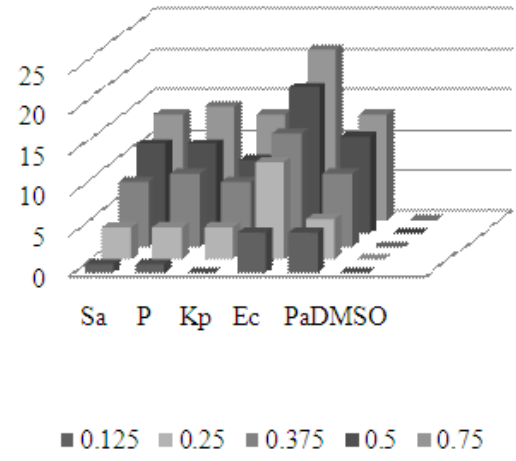


Figure 5. The antibacterial activity of coumarins (Dutta et al., 1986).

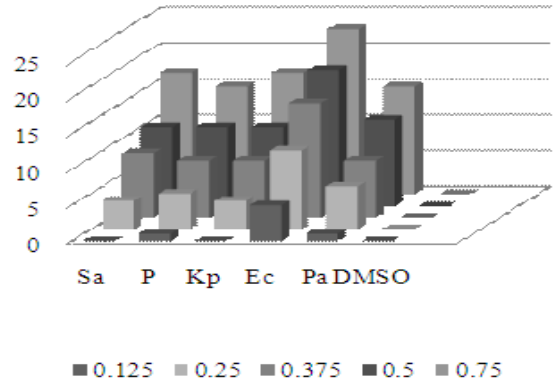


Figure 6. The antibacterial activity of coumarins (Hoult and Paya, 1996).

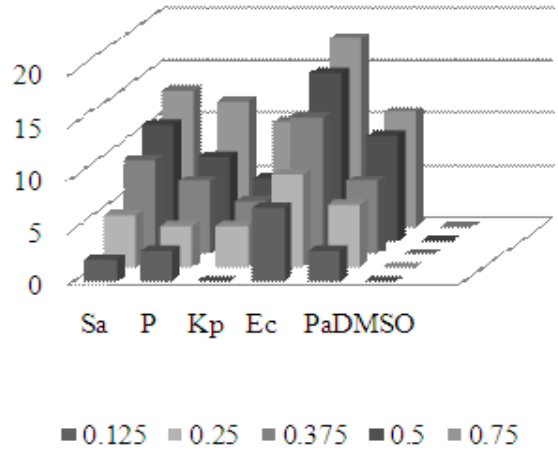


Figure 7. The antibacterial activity of coumarins (Amiery, 2007).

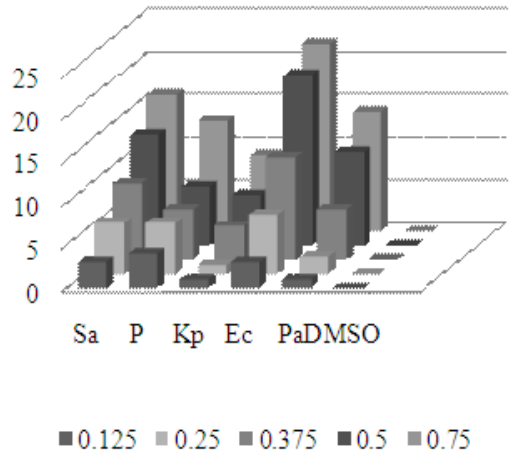


Figure 8. The antibacterial activity of coumarins (Habib, 2006).

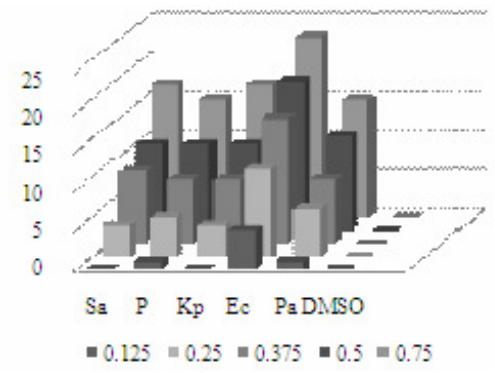


Figure 9. The antibacterial activity of coumarin [18].

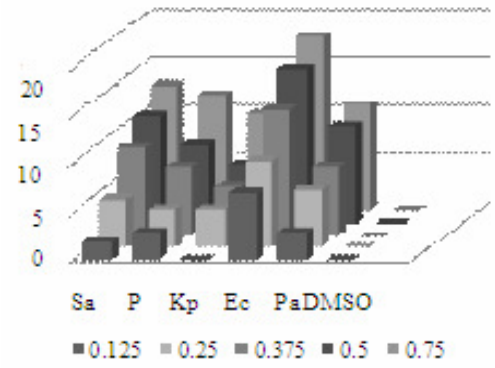


Figure 10. The antibacterial activity of coumarin [19].

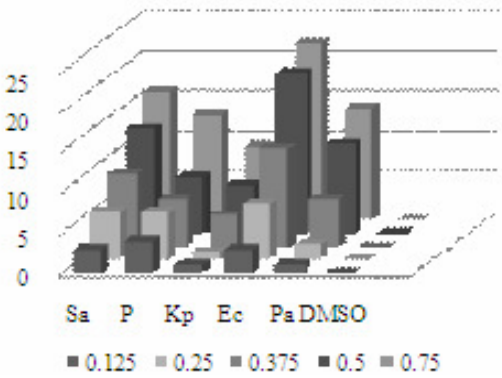


Figure 11. The antibacterial activity of coumarin [20].

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