Addition of Active Methylene Compounds to Schiff Bases and Study the Antibacterial Activity of the Products

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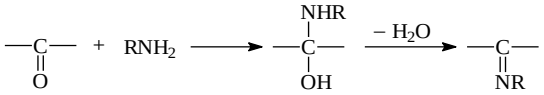
Abstract:
A series of Schiff bases (1-10) had been prepared by the condensation of aniline with benzaldehyde and their substituted isomers which in turn condensed with cyclohexanone to afford (11-20), the self condensation of the later compounds afforded a series of compounds (21-28). The suggested structures of the final products were supported depending on some valid physical properties and spectral data. Theoretical calculations had also been used to support the suggested mechanisms. The antibacterial activity against (10) types of bacteria of some products also had been tested.

Keywords: active methylene compounds, Schiff bases, antibacterial

Introduction:

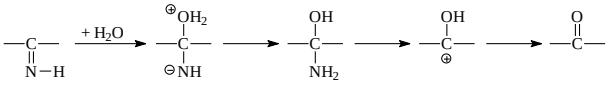
Several methods had been used for the preparation of Schiff bases, such as the addition of amines to aldehydes or ketones[(1a)]:



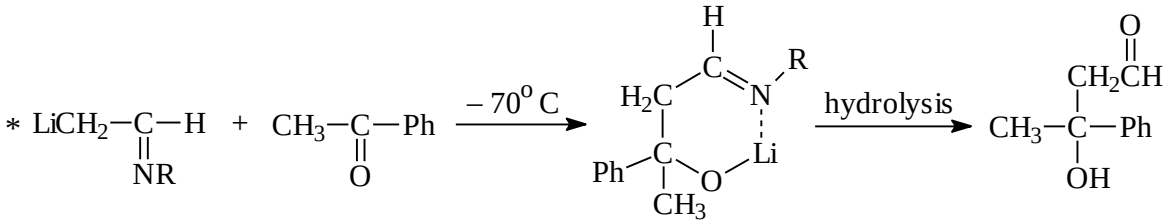
Schiff base

Or by the reduction of nitrilium ions, isocyanide[(1b)], and by the rearrangement of alkyl azides, Steiglitz rearrangement[(1c)].

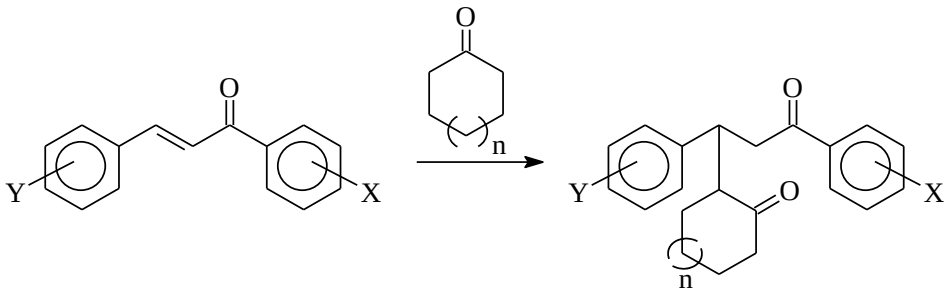
The hydrolysis of Schiff bases leads to the original carbonyl compound which is used to synthesize the imine[(2)]:



The condensation of active hydrogen compounds (such as cyclohexanone in the present work) with Schiff base may also be used to add the □-carbon of an aldehyde* to the carbonyl carbon of the ketone[(3)] as shown:

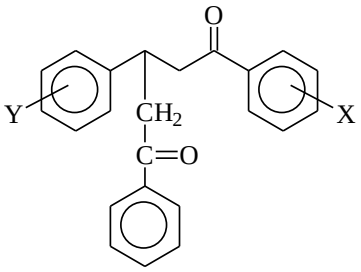


The cyclic ketones (cyclopentanone, cyclohexanone, cycloheptanone and cyclooctanone) were used as an active hydrogen compounds to be added to the double bond of an □,□-unsaturated ketone (chalcone) in a Michael addition manner[(4)]:



X: H, p-Cl, Y: H, p-MeO, n = 0, 1, 2, 3

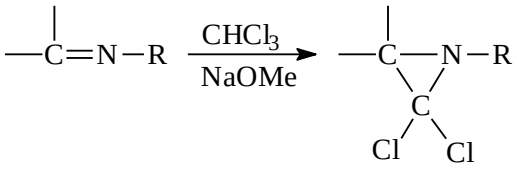
In the same way (Michael addition), acetophenone may also react with the chalcone[5]:



X: H, p-Me ; Y: H, p-

The carbon-carbon double in chalcones exposed to the active methylene compounds to undergo a nucleophilic addition under basic conditions through the Michael route which is quite similar to the addition of nucleophile (cyclohexanone anion) to the carbon-nitrogen double bond of the Schiff bases (the present work).

Schiff bases may also be used to afford heterocyles like substituted aziridines[6]:



Experimental:

General:

Melting points were determined on an Electrothermal 1A 9000 Digital-Series 1998 apparatus and are uncorrected. Infrared spectra (KBr pellets) were measured on a Shimadzu 8400 FTIR spectrophotometer. Ultraviolet spectra were recorded on a Shimadzu UV-Visible spectrophotometer UV-160. On the basis of the data obtained from the minimized geometry, theoretical calculations were computed in CS ChemOffice molecular modeling package using semi-empirical AM1 module.

Chemical part

Preparation of Schiff bases (1-10)

General procedure[7]

A solution of equimolar of aniline, benzaldehyde or their substituted aniline and benzaldehyde (0.01 mole) in (10 ml) n-butanol were heated for a while (10-20 min.) in a 100 ml beaker at about (100 ^{o}C). Cooling the reaction mixture gave the precipitate of the corresponding Schiff bases (recrystallized from ethanol). Physical properties and spectral data were illustrated in Table (1). The spectral data were in an agreement with the reported values[8,9].

The nucleophilic addition of cyclohexanone carbanion to Schiff bases, the products (11-20).

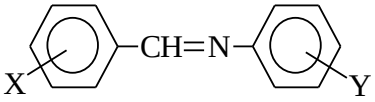
General procedure[10]

A mixture of cyclohexanone (0.01 mole) and (1 ml) of 1.5% ethanolic NaOH was stirred for (15 min), then (0.01 mole) of desired Schiff base was added. The reaction mixture was kept under reflux for (2 hrs), then cooled, the resulted solid were recrystallized from ethanol. Table (2) illustrates some physical properties and valid spectral data which in comparison with the reported values[8,9] seemed in a good agreement.

The self condensation of the products (11-20) to afford the final products (21-28):

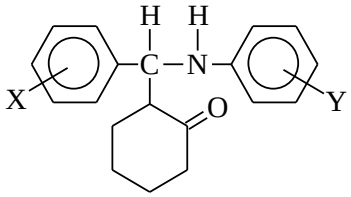
The alkaline solution of (0.01 mole) of the desired substituted cyclohexanone in (25 ml) ethanol and (0.5 ml) ethanolic 5% sodium hydroxide was refluxed for (4 hrs) till the change in colour is ceased. The reaction mixture was then cooled in a refrigerator, the solid products then filtered, dried and recrystallized from ethanol. Table (3) shows some physical properties and spectral data of the final products (21-28).

Table (1): Physical properties and spectral data of Schiff bases (1-10)



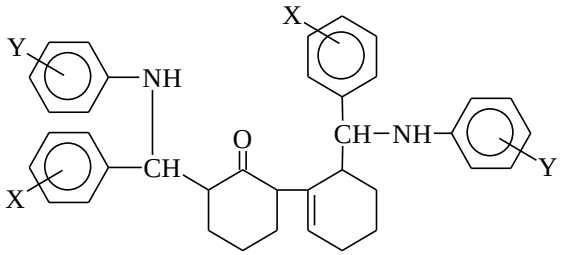
No.	X	Y	m.p. (°C)	Yield (%)	Colour	U.V (EtOH) λ_{max} (nm)	I.R (KBr) ν (cm^{-1}) C=N
1	H	H	41-43	82	Destinct yellow	298	1655
2	H	2,5-Cl	78-80	78	Yellow	306	1660
3	H	4-NO_2	73-74	88	Yellow	378	1645
4	3-NO_2	H	58-59	64	Yellow	296	1632
5	4-OMe	H	40-41	77	Yellow	290	1648
6	3-NO_2	2,5-Cl	108-110	60	Yellow	306	1650
7	3-NO_2	4-NO_2	140-142	58	Deep yellow	378	1675
8	4-OMe	4-NO_2	116-118	80	Deep yellow	336,360	1662
9	4-OMe	2,5-Cl	80-81	85	Yellow	300	1638
10	4-OMe	2,4-Cl	139-140	67	Grey	326	1650

Table (2): Physical properties and spectral data of (11-20)



No.	X	Y	m.p. (°C)	Yield (%)	Colour	U.V (EtOH) λ_{max} (nm)	I.R (KBr) ν (cm^{-1})	
							C=O	N-H
11	H	H	284 D	45	White	242	1635	3450
12	H	2,5-Cl	-	35	Yellow	240	1630	3452
13	H	4-NO_2	166-168	65	Green	242	1633	3455
14	3-NO_2	H	300 D	50	Brown	240	1638	3450
15	4-OMe	H	215 D	40	Deep brown	244	1637	3462
16	3-NO_2	2,5-Cl	98-100	35	Deep brown	244	1637	3450
17	3-NO_2	4-NO_2	290-291	55	Yellow	242	1632	3481
18	4-OMe	4-NO_2	122-124	60	Green	242	1633	3482
19	4-OMe	2,5-Cl	230 D	75	Yellow	244	1636	3452
20	4-OMe	2,4-Cl	230-232	80	Yellow	244	1637	3452

Table (3): Physical properties and spectral data of final products (21-28)



No.	X	Y	m.p. (°C)	Yield (%)	Colour	U.V (EtOH) λ_{max} (nm)	I.R (KBr) ν (cm^{-1})		
							C=C	C=O	N-H
21	H	H	350 D	40	White	266	1635	1669	3421
22	H	4-NO_2	225 D	80	Yellow	284	1632	1670	3451
23	3-NO_2	H	250 D	75	White	280	1576	1680	3443
24	4-OMe	H	230 D	70	Brown	350	1640	1682	3442
25	3-NO_2	4-NO_2	210 D	65	Yellow	348	1638	1673	3449
26	4-OMe	4-NO_2	290 D	85	Yellow	284	1631	1666	3450
27	4-OMe	2,5-Cl	252 D	60	White	282	1639	1670	3441
28	4-OMe	2,4-Cl	360 D	55	White	284	1578	1671	3423

Microbiological part

I. Preface

The biological inhibitory effect of the final products (21-28) against ten types of bacterial groups (Gram-negative) and (Gram-positive) was studied and investigated in the present work (Table 4). The isolates were identified in Biology Dept., College of Science in Mosul University. The standard Kirby and Bauer[11] method was used.

II. Method

The bacterial species (loopful) were cultured in a nutrient broth and incubated for (14-16 hr) at a temperature of (37 °C), then distributed on the nutrient agar by a sterile swab.

The plates were incubated at (37 °C) for (30 min). A Whatman No. 1 filter paper discs were distributed on the agar and a certain equal (1 mg/1 ml) or (1 ml/ 1 ml) of the product/solvent (DMSO) was added. The control here were the Ciprofloxacin and/or Ampicillin for comparison, the plates were then incubated at (37 °C) for (18-24 hr).

The results were interpreted according to the diameter (mm) of the inhibition zone appeared around the discs[12], depending on the report of the WHO. The resistant (R) result represented the diameter of inhibition < (11 mm). However, the moderately sensitive (MS) result was regarded when the zone of inhibition was between (12-16 mm). The sensitive (S) result was > (16 mm).

Results And Discussion:

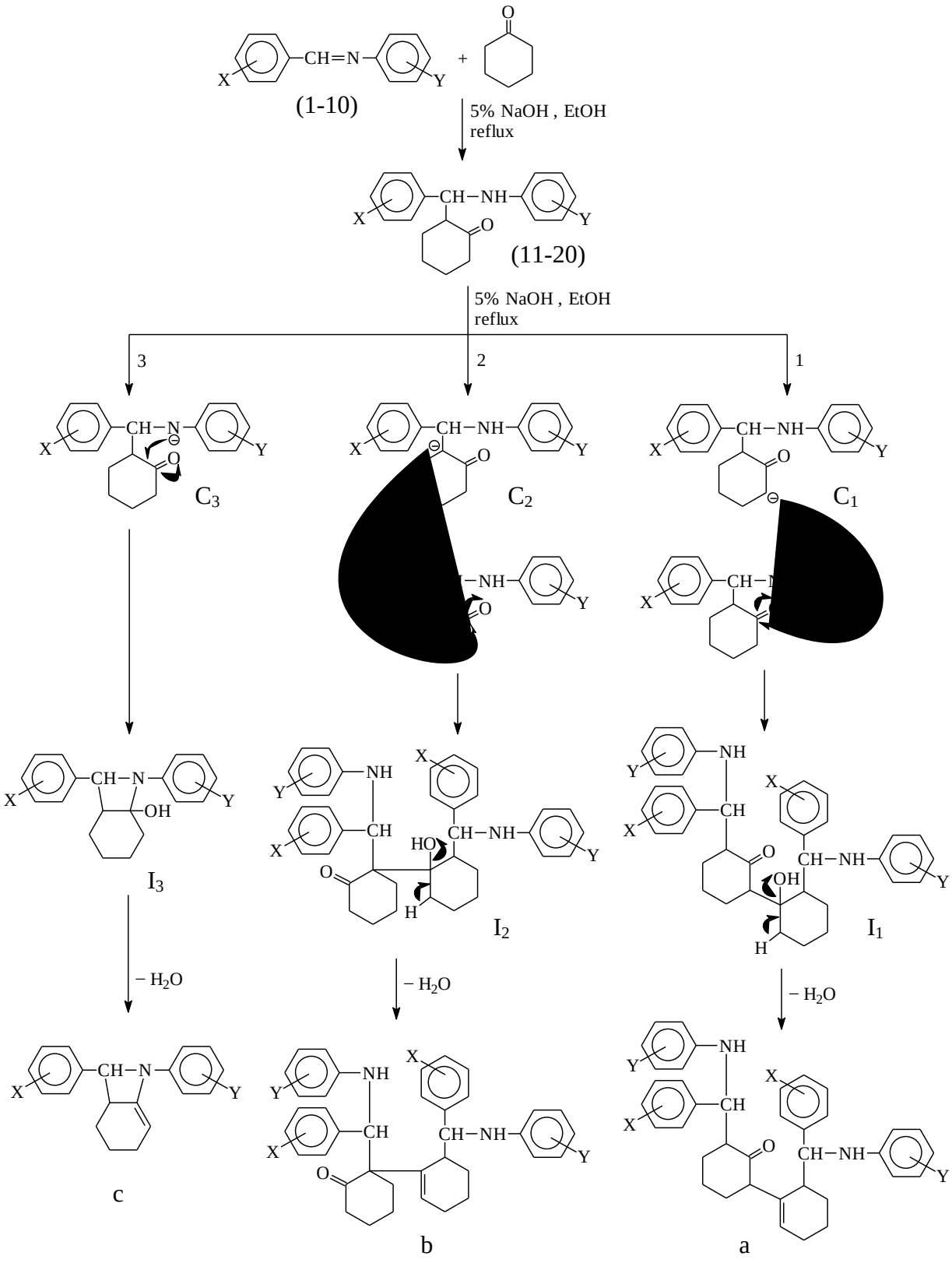
I. Chemical part

The condensation of anilines and benzaldehydes leads to the corresponding Schiff bases[13,14].

The UV spectra[15] of Schiff bases (1-10) showed a maximum absorption in this region at the range of (290-378 nm), Table (1), but the intermediate products (11-20) exhibit arrange of (240-244 nm) which means a blue shift (shift to a shorter wavelength), Table (2), this may be related to the absence of the conjugation which was effective in the absorption of Schiff bases. On the other hand, the final products (21-28), Table (3), manifest a range of (266-384 nm) which may be interpreted by the presence of an additional aryl groups, so their absorption was at a higher wavelength compared with the intermediates (11-20).

The IR spectra[16] of the final products (Table 3) exhibit a stretching vibration at the range of (1640-1631 cm^{-1}) related to the carbon-carbon double bond region, whereas the range of (1682-1666 cm^{-1}) belongs to the carbonyl stretching vibration. Finally, the nitrogen-hydrogen stretching vibration seemed at the range of (3451-3421 cm^{-1}).

The suggested mechanism[17] of the anionic addition of cyclohexanone to Schiff bases (1-10) leads to the intermediate products (11-20) (Scheme 1), which under basic conditions may lead to the three expected anions C_1, C_2 and C_3, which in turn may undergo self-condensation to afford the intermediates I_1, I_2 and I_3, which among the loss of a water molecule produced the corresponding expected final product a, b and c. The substituted azetine (c) is neglected due to two factors (Table 5).



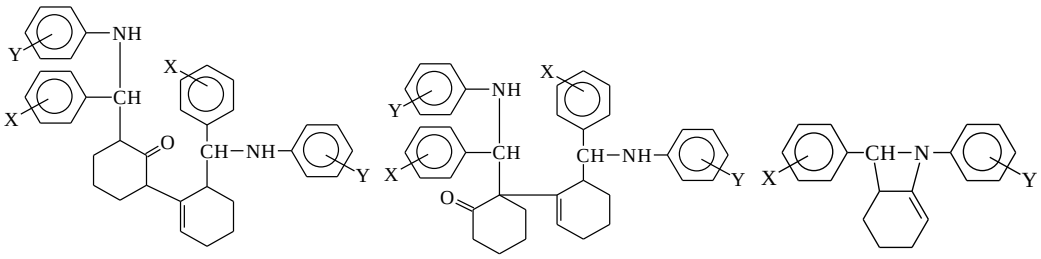
a. The ring strain.

b. The absence of carbonyl group which is found according to two ways:

I. The IR spectra. II. Group test (2,4-DNPH) test.

Scheme (1): The condensation of cyclohexanone with Schiff bases followed by the self condensation of the products C_1, C_2 and C_3

Table (5): The heat of formation (H.F) and the steric energy (S.E) for compounds (21-28) with the probable structures a, b and c



(a) (b) (c)

Comp. No.	X	Y	H.F. Kcal/mole	S.E Kcal/mol
21a	H	H	100.99114	18.162
21b	H	H	133.35910	35.532
21c	H	H	115.40426	46.154
22a	H	4-NO_2	400.93460	60.573
22b	H	4-NO_2	138.94347	125.374
22c	H	4-NO_2	116.23560	96.799
23a	3-NO_2	H	225.92932	31.957
23b	3-NO_2	H	271.52574	55.964
23c	3-NO_2	H	112.74008	87.630
24a	4-OMe	H	31.89002	41.848
24b	4-OMe	H	57.54634	68.087
24c	4-OMe	H	71.37884	75.906
25a	3-NO_2	4-NO_2	627.23443	114.563
25b	3-NO_2	4-NO_2	118.19051	148.923
25c	3-NO_2	4-NO_2	115.42832	123.380
26a	4-OMe	4-NO_2	314.23924	87.119
26b	4-OMe	4-NO_2	43.29475	124.560
26c	4-OMe	4-NO_2	76.05690	110.793
27a	4-OMe	2,5-Cl	17.29733	68.439
27b	4-OMe	2,5-Cl	42.09353	82.651
27c	4-OMe	2,5-Cl	72.57387	61.676
28a	4-OMe	2,4-Cl	16.64089	67.755
28b	4-OMe	2,4-Cl	46.14862	73.159
28c	4-OMe	2,4-Cl	65.40227	67.078

Although the H.F of C is the least (Table 5), now, in a comparison of a and b, it was found that (for 21, 23, 24, 27 and 28):

I. The H.F for a is less than that for b.
II. The bulk effect, that is to say the isomer b is substituted on one side of the cyclohexanone carbonyl, while the substitution of isomer a is balanced on the two sides of cyclohexanone carbonyl, that leads to less steric effect.

II. Microbiological part

The results showed the *E. coli* was sensitive to 28 and moderately sensitive to 21, 22 and 27, but resistant to 23, 24, 25 and 26. While *Kleb. pneumoniae* was moderately sensitive to 27 and resistant to 21, 22, 23, 24, 25, 26 and 28. Whereas *Proteus sp.* was sensitive to 24 and resistant to the rest of the tested final products. But *Serratia marcescers* was sensitive to 27 and moderately sensitive to 26 and 28 but resistant to the others. The *Neisseria sp.* was resistant to 21, 27 and 28, but moderately sensitive to the rest. *Sal. typhi* Was resistant to 21, 22 and 27, but moderately sensitive to others. *Pseu. aeroginosa* was resistant to 22, 23 and 26, but moderately sensitive to 21, 24, 25, 27 and 28. *Staph. aureus* and *Bacillus sp.* were seemed to be resistant to all tested final products.

Table (4): Inhibition effects of the final products (21-28) on growth of some Gr^- and Gr^+ bacteria

Test organism	Compound number								Antibiotic
	21	22	23	24	25	26	27	28	
E. coli	MS	MS	R	R	R	R	MS	S	MS
K. pneumoniae	R	R	R	R	R	R	MS	R	MS
Proteus sp.	R	R	R	S	R	R	R	R	S
Serratia marcescens	R	R	R	R	R	MS	S	MS	S
Neisseria sp.	R	MS	MS	MS	MS	MS	R	R	-
Salmonella typhi	R	R	MS	MS	MS	MS	R	MS	-
P. aeroginosa	MS	R	R	MS	MS	R	MS	MS	S
Staph. aureus	R	R	R	R	R	R	R	R	S
Strep. Faecalis	R	R	MS	R	R	R	MS	MS	-
Bacillus sp.	R	R	R	R	R	R	R	R	R

S: Sensitive, MS: Moderately Sensitive, R: Resistant

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اضافة مركبات المثيلين الفعالة الى قواعد شيف ودراسة فعالية النواتج المضادة للبكتريا

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(تاريخ الاستلام: / /٢٠٠٧ ، تاريخ القبول: / / ٢٠٠٧)

الملخص:

تم تحضير سلسلة من قواعد شف (١-١٠) من تكاثف الانيلين والانيلين المعوض مع البنزالديهايد المعوض والتي ادخلت بتكاثف مع الهكسانون الحلقي للحصول على المركبات (١١-٢٠) وعند السماح للاخيرة بالتكاثف الذاتي فانه ينتج سلسلة من المركبات (٢١-٢٨). تم دعم التراكيب المقترحة للنواتج النهائية بالاعتماد على بعض الصفات الفيزياوية والبيانات الطيفية المتاحة. لقد استخدمت الحسابات النظرية لدعم الميكانيكيات المقترحة كما تم فحص فعالية بعض هذه المركبات كمضادات لعشرة انواع من البكتريا.

الكلمات المفتاحية: مركبات المثيلين الفعالة، قواعد شيف، الفعالية المضادة للبكتريا.