Synthesis and Bioassay of Novel Quinozolins

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Novel Quinozolins were synthesized in a good yield through convert lacton to lactam and study the biological activity of the synthesized compounds. Quinozolins were characterized by elemental analysis, FT-IR and UV/visible spectra. The novel Quinozolins 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 Quinozolins 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 Quinozolins derivatives through the replacement of oxygen atom by nitrogen atom.

Introduction:

The coumarins can be roughly categorized as the following [3]:

- 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 [4-17]. 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 [18]. A valuable method for the synthesis of coumarins is the Pechmann reaction, of phenols, using concentrated sulfuric acid as the catalyst [24]. By-products are formed and the reaction needs a long time, and introduces corrosion problems [25]. For these reasons there have been some attempts to find alternative environmentally benign synthetic routes. Nafion-H, [26] amberlyst 15, [27] montmorillonite clay, [28] and other

solid acids14 have been employed for this purpose in the Pechmann condensation. Some organic acids and metallic Lewis acids are also examined in this transformation [29]. 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[30].

Experimental: All chemical used were of reagent grade (supplied by either Merck or Fluka) and used as supplied. FT-IR spectra were recorded using shimadzu-8300 spectrophotometer using KBr. Electronic spectra were recorded using shimadzu uv–vis. spectrophotometer type 160A in the range 200-800nm.

Synthesis of compound (1): Mixture of creatine (2.62 g, 0.02 mol) (2-(1-methylguanidino)acetic acid) with 50 ml absolute ethanol, and 2.5ml concentrated sulfuric acid was refluxed for 4hrs., yield 50% of compound (1).

Synthesis of Compound (2): Solution of (0.035 mole) coumarin and compound (1) (0.07mole) in benzene was refluxed for 6 hours , the solvent was concentrated and the separated solid product was filtered and washed with cold ethanol, and recrystallized from ethanol-water.

Synthesis of compound (3): compound (3) was synthesized by the addition of hydrazine hydrate (3.4mL., 0.069mole) to (0.069mole) of compound (2) with stirring then the mixture was refluxed for 1hr. then cooled. Absolute ethanol (50mL.) was added and the mixture was refluxed again until the product was filtered off and recrystallized using ethanol.

Synthesis of compound (4 and 9): A mixture of **(3 or 5)** (0.5 mmol) and CS2 (2.5 mmol) in ethanolic KOH (5 mL) was refluxed for 6 h. After cooling, the mixture was poured into ice/water, the yellow precipitate was filtered off, washed with water and recrystallized from acetone.

Synthesis of compound (5): A mixture of **(3)** (0.5 mmol) and CS2 (2.5 mmol) in hydrazin 5mL. was refluxed for 6 h. After cooling, the mixture was poured into ice/water, the yellow precipitate was filtered off, washed with water and recrystallized from acetone.

Synthesis of compound (6): A mixture of **(2)** (0.5 mmol) and thiosemicarbazide (0.5 mmol) was refluxed for 2-3 h. After cooling, the yellow precipitate was filtered off, washed with water and recrystallized from ethanol.

Synthesis of compound (7): Reflux of compound 6 with ethanol for 6 h. After cooling, the yellow precipitate was filtered off, washed with water and recrystallized from acetone.

Synthesis of compound (8): A mixture of **5** (0.5 mmol) and $POCl_3$ (10 mL) was refluxed at 100 ^{o}C for 2 h. After cooling, the excess of $POCl_3$ was removed under reduced pressure and the residue was treated with saturated solution of K_2CO_3 under ice cooling.

Synthesis of compound (12-16) Schiff bases: A mixture of compound 3 (0.005 mol) and the (0.005 mol) aromatic carbonyl was refluxed in absolute ethanol 25 ml for 6-8 hr. The reaction mixture was cooled and the product obtained was recrystallized from ethanol.

Synthesis of compound (11): A mixture of compound 4 (0.005 mol) and the (0.005 mol) anthranilic acid was refluxed in absolute ethanol 25 ml for 24 hr. The reaction mixture was cooled and the product obtained was recrystallized from acetone.

Antibacterial activity: The Test Organisms used were: *Staphylococcus aureus* as gram positive bacteria, and *Escherichia coli*, *Proteus vulgaris*, *Klebsiella and Pseudomonas aeruginosa* as gram negative bacteria. Hole diffusion method was used to measure the inhibitory activity as indicated by the diameter of the inhibition zone. Concentration of 1mg/mL of test compounds were prepared by dissolving the compounds in dimethyl formamide (DMF), for each concentration, 0.2 ml of synthesized compounds 6,10,12,14 and 15 (1 mg/ml) was added to each hole. The plates were allowed to stand at room temperature for two hours and then incubated. The organisms were grown in nutrient agar at 37°C for 24 hours. After incubation period, the growth inhibition zones diameters were carefully measured in mm. The clear zone around the wells was measured as inhibition zones. The absence of a clear zone around the well was taken as inactivi

Table 1: Physico analytical data for the Synthesized of compounds

No.	Names	M.P.C	Yield	Color
1.	ethyl 2-(1-methylguanidino)acetate	oily	50%	yellow
2.	ethyl 2-(N-methyl-2-oxo-1,2-dihydroquinoline-1-carboximidamido)acetate	oily	60%	milky
3.	N-(2-hydrazinyl-2-oxoethyl)-N-methyl-2-oxoquinoline-1(2H)-carboximidamide	65_67	45%	yellow
4.	N-(5-mercapto-1,3,4-thiadiazol-2-yl)-N-methyl-2-oxoquinoline-1(2H)-carboximidamide	105_107	33%	Light brown
5.	N-(5-hydrazinyl-4H-pyrazol-3-yl)-N-methyl-2-oxoquinoline-1(2H)-carboximidamide	68_70	55%	Light brown
6.	2-(2-(N-methyl-2-oxo-1,2-dihydroquinoline-1-carboximidamido)acetyl)hydrazinecarbothioamide	123-125	45%	yellow
7.	N-methyl-2-oxo-N-((5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)quinoline-1(2H)-carboximidamide	60-62	55%	orange
8.	N-(5-(1,2,3-oxadiazol-2(5H)-yl)-4H-pyrazol-3-yl)-N-methyl-2-oxoquinoline-1(2H)-carboximidamide	oily	35%	Light brown
9.	N-methyl-2-oxo-N-(5-(2-thioxo-1,3,4-thiadiazol-3(2H)-yl)-4H-pyrazol-3-yl)quinoline-1(2H)-carboximidamide	oily	50%	black
10.	2-(5-(N-methyl-2-oxo-1,2-dihydroquinoline-1-carboximidamido)-1,3,4-thiadiazol-2-ylamino)benzoic acid	93-95	45%	brown
11.	(Z)-N-(2-(2-(3-hydroxybenzylidene)hydrazinyl)-2-oxoethyl)-N-methyl-2-oxoquinoline-1(2H)-carboximidamide	150-152	25%	dark brown
12.	(Z)-N-(2-(2-(1-(3-hydroxyphenyl)ethylidene)hydrazinyl)-2-oxoethyl)-N-methyl-2-oxoquinoline-1(2H)-carboximidamide	82-84	55%	yellow
13.	(Z)-N-(2-(2-(3-(dimethylamino)benzylidene)hydrazinyl)-2-oxoethyl)-N-methyl-2-oxoquinoline-1(2H)-carboximidamide	100-102	50%	orange
14.	N-methyl-2-oxo-N-(2-oxo-2-(2-(pyrrolidin-2-ylidene)hydrazinyl)ethyl)quinoline-1(2H)-carboximidamide	oily	30%	Light yellow
15.	N-(2-(2-(2-imino-1-methylimidazolidin-4-ylidene)hydrazinyl)-2-oxoethyl)-N-methyl-2-oxoquinoline-1(2H)-carboximidamide	99-101	45%	white

Table 2. Infrared absorption frequencies (cm^{-1}) of the synthesized compound

No.	UV-visible nm	FT-IR spectroscopy (cm^{-1})						
		v(NH2)	v(N–H)	v(C-H) arom.	v(C-H) aliph	v(C=N)	v(C=O)	v(S-H)
1	320	3300	3050	-------	2927.5	1590	1697	-------
2	320،340	-------	3090	3095	2910	1610	1590.5	-------
3	340،360	3230	3040	3070	2817	1605	1695	-------
4	315	-------	3045	3060	2925	1625	1697	3427
5	320	3350	------	3090	------	1620	1690	3425
6	345	3370	3050	3095	2910	1625	1698	-------
7	330	-------	3055	3080	-------	1615	1690	-------
8	340	-------	-------	3090	-------	1610	1680	-------
9	350	-------	-------	3095	-------	1625	1690	3430
10	320	3350	-------	3080	-------	1620	1680	-------
11	340	-------	3090	3050	-------	1590.5	1595	-------
12	325	-------	3075	3060	-------	1610	1610	-------
13	315.5	-------	3050	3040	-------	1605	1620	-------
14	331	-------	3090	3060	-------	1615	1615	-------
15	320	-------	3075	3040	-------	1617	1610	-------

Table 3. Antimicrobial activity of novel synthesized compounds

No.	Bactria				
	Staphylococcus aurous	***E.coli***	***Proteus vulgaris***	***Pseudomonas***	***Klebsiella***
S_6	++	+++	+++	+	++
S_{10}	+	++	++	--	+
S_{12}	+++	+	+++	--	+
S_{14}	--	--	+	+	--
S_{16}	+	+	+	+	--

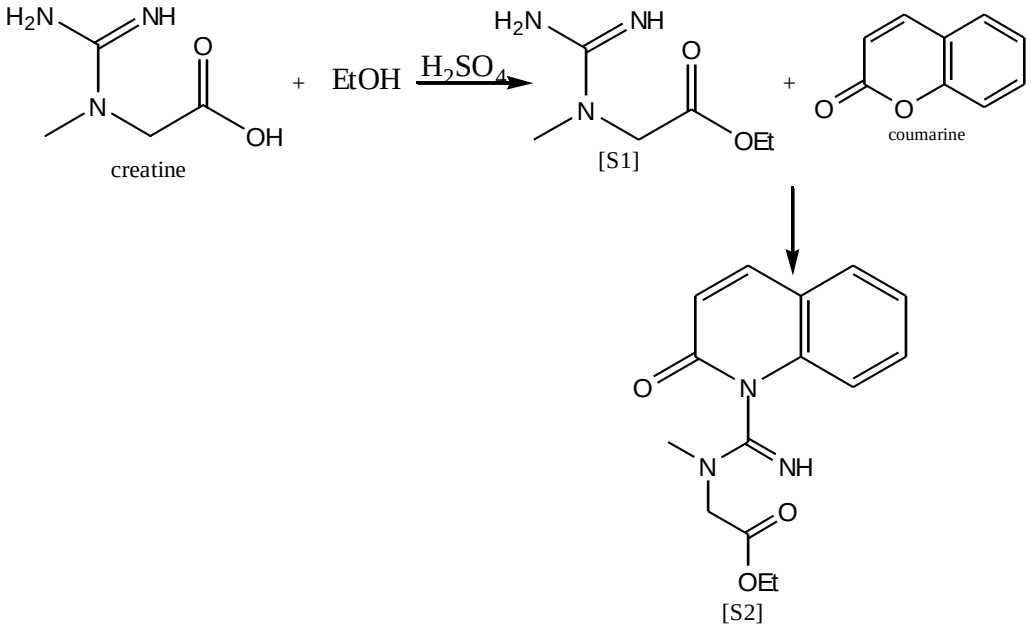
+=6-10 mm, ++=11-15 mm, +++=16-25 mm.

Biological Activity: The antimicrobial screening data show that the compounds exhibit antimicrobial properties and it is important to note that the new derivatives exhibit more inhibitory effects than the orginal molecule (I). From table (2) it is clear that the zone of inhibition against the gram-negative bacteria and gram-positive bacteria. The increased activity of the new derivatives can be explained that act as more powerful and potent bactericidal agents, thus killing more of the bacteria than the orginal molecule (I). The π-electron delocalization over the new derivatives increases the lipophilic character and favours its permeation through the lipoid layer of the bacterial memberanes. It was reported that 3*H*-quinazolin-4-one derivatives have interesting antimicrobial activity against different species of Gram positive bacteria, Gram negative bacteria and pathogenic Fungi. Schiff's bases have been widely reported to be biologically versatile compounds having antifungal, fungicidal, herbicidal and plant growth regulating properties. The presence of imino linkage (-N=C-) in these compounds has been regarded as being assential for the enhancement of antibacterial and antimicrobaial activities(Rajesh, and Greech, 1988; Dash and others, 1984; Miklabiv and

others, 1986; Waisser and others, 2007; Caroll and others, 1997; Guersoy, and Illhan, 1995; Pandeya and others, 1999; Grover, and Kini, 2006; Kunes and others, 2000; Waisser and others, 2003; Waisser and others, 2003).

Results and discussion:-

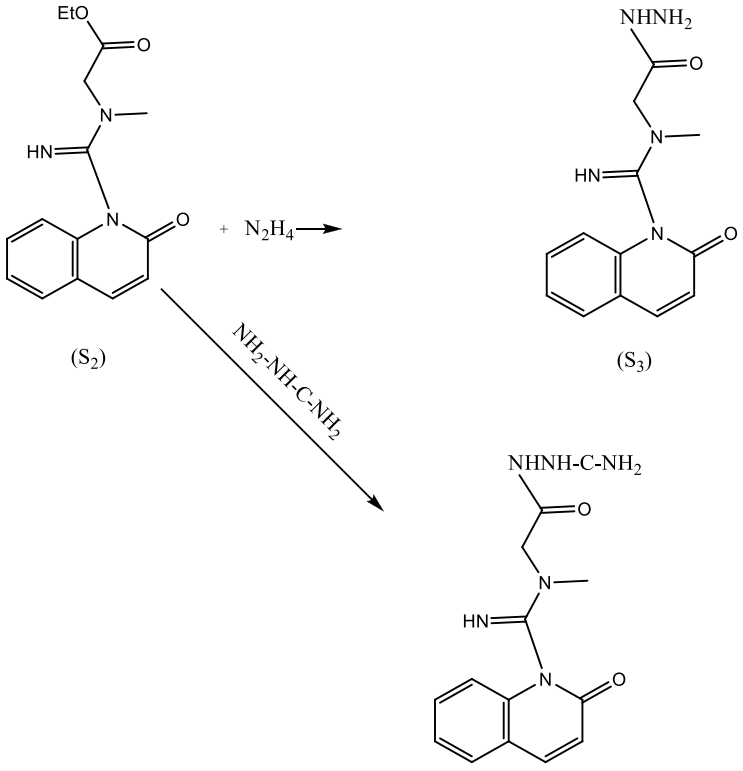
Reaction of creatine with ethanol in acidis mediem led to the for mation of compound (S_1)then the compound (S_1) reacte with coumarine to give compound (S_2) . (scheme1).



The FT-IR spectroscopy showed that the peak of (NH_2) groups are dis appeared and appearance of (C-N) peak . new absorpti on bands at (1720-1700 cm-1) for (C=O) ، the UV. Spectrum of the (S_1) have been measured in aceto nitrile and show two absorption bands at (230 nm for π-π*) transition and (305 nm) for (n-π*) transition ، the UV. Spectrum of the (S_2) have been measured in acetonitrile and show two asorption bands at (244.5 nm for π-π*) transition and (360.5 nm) for n-π* transition .

Synthesis of S_3 and S_6 compounds :-

The compound (S_2) reacte with hydrazine hydrade to give the compound (S_3) and compound (S_2) reacte with thiosem carbazide to give compound (S_6) (Schem2).

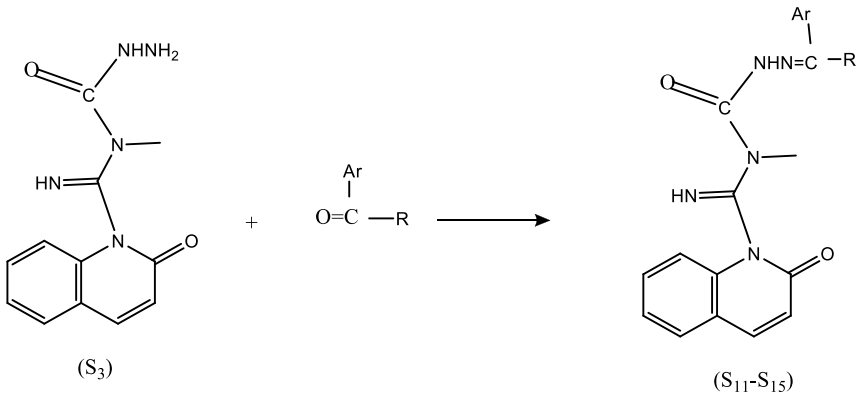


(S_2) (S_3) (S_4)

The FT-IR spectroscopy showed that the peak of (C-O) are disappeared and appearance of (NH_2) peak and the (N-H) peak ، new absorption bands at (3200-3350 cm) for (NH_2) and (NH) at (3050 cm) to the compound (S_3) and (S_4) ، the(UV). Spectrum of (S_3) have been measured in acetonitrile acetonitrile and show two absorption bands at (230 nm) for (π-π*) Transition and (305 nm) for (n- π*) transition ، the(UV) . spectrum of the (S_4) have been measured in (360.5nm) for (n- π*) transition .

Synthesis of Schiff bases (S_{11}-S_{15})

Schiff bases were prepared by condensation of an appropriate aromatic aldehydes or ketones with (S_3) according to the reported procedure ، the prepared compounds were identified by (UV- visible) and FT-IR spectrum ، and used immediately in the reactions as fllows (schem 3)



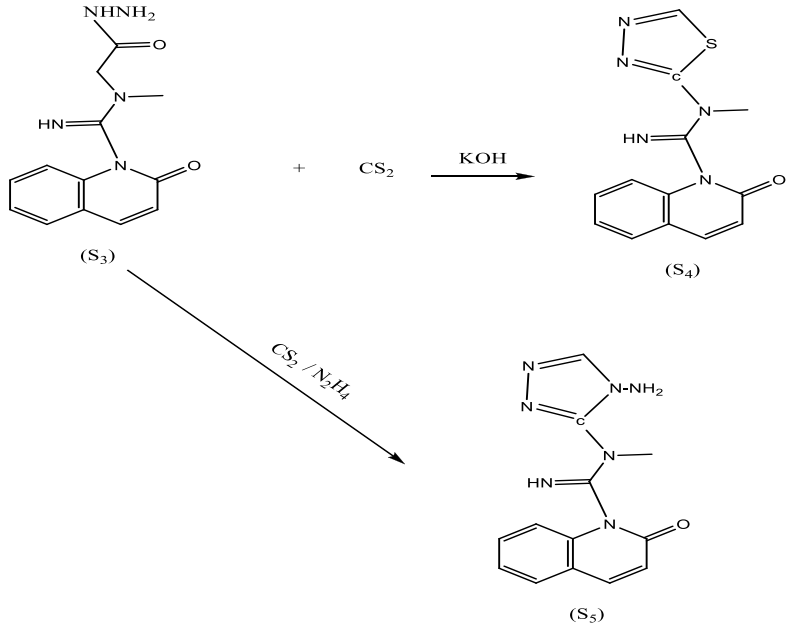
(S_3) (S_{11}-S_{15})

The aromathic aldehyde and ketone are (m-hydroxy benzaldehyde ,p-hydroxy benzaldehyde,dimethyl amine benzaldehyde ,pyrollidone, creatinine .

The FT-IR spectroscopy showed that the absorbtion bands due to (NH_2) were disappeared and anew absorption bands appeared at (1590-1617 cm^{-1}) for (C=N) and absorption bands at (3088 cm^{-1}) for (N-H)

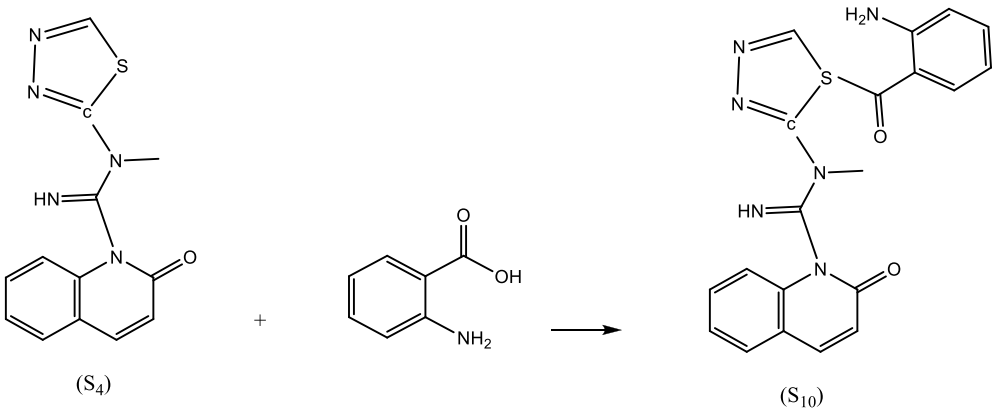
Reaction of (S_3) with (CS_2) to form (S_4، S_5) respectively :-

Heating the mixture of compound (S_3) with(CS_2) hn ethanolic solution with (KOH) to give the crystale compounds (S_4) then this reaction repeat after put hydrazine hydrate with the mixture to give the compound (S_5) and the FT-IR spectroscopy showed that the absorption bands of (C=O) disappeared and appearance of (S-H) in compound (S_4) and appearance of (NH_2) in compound (S_5) at (3427cm) and anew band appeared at (1280cm^{-1}) for (N-N=C) for compound (S_4) .(Schem 4) .



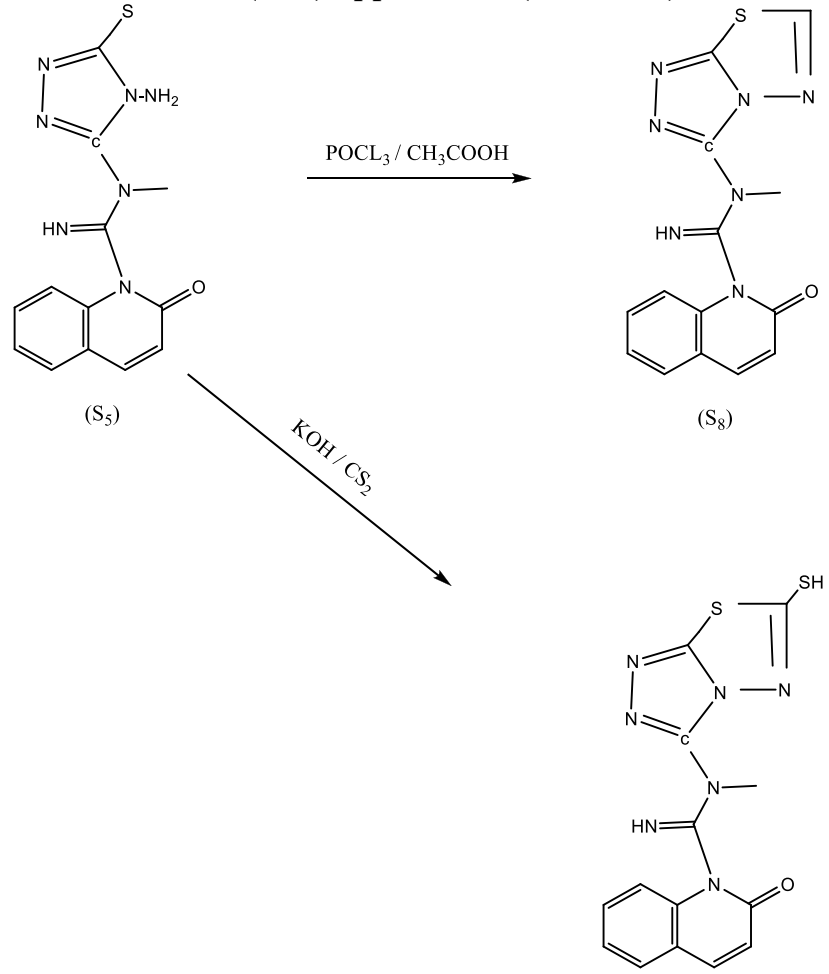
Reaction of (S_4) with anthranilic acid to form (S_{10}).

The FT-IR of this compound appeared at (3200-3350 cm) for (NH_2) and anew band appeared at (1641 cm) for (C=O) and disappeare the band of (S-H).



Reaction of (S_5) with pocl3 and with CS_2 to form (S_8 and S_9) respectirely.

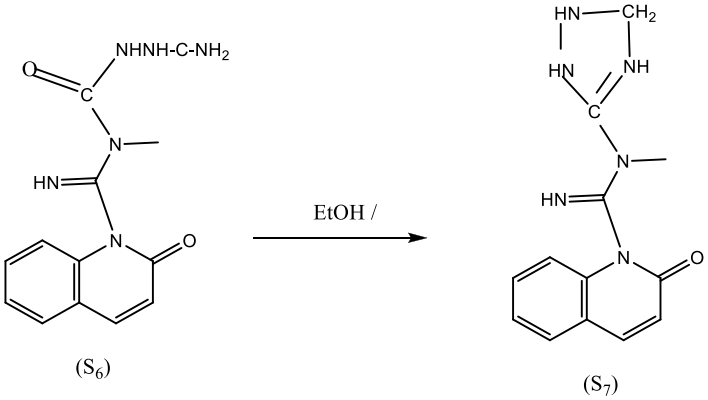
The FT-IR spectrum of the compound (S_9) Showed disappear of the band (NH_2) and new band appeared at (3050 cm) of (N-H) and(1392 cm) of (C=S) ، and the FT-IR spectrum of compound (S_8) is showed disappear the band of (NH_2) and new band of (C-S) appeared at (1100cm) .



(S_5) (S_8) (S_9)

Reaction of (S_6) with ethanol to form (S_7)

The FT-IR Spectrum of this compound (S_7) showed disappeared of the band (C=O) and (NH_2) and appeared of new band of (C=N) in (1530- 1610 cm) and the band of (N-H) at (3090 cm).



(S_6) (S_7)

The uv.spectrum of (S_7) have been measured in acetonitrile and show absorbtion bands at (235nm for (π-π*) Transition and (308 nm) for (n- π*) transition .

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تحضير ودراسة الفعالية البايولوجية لبعض مركبات الكوينوزولين

ياسمين كاظم الماجدي

فرع التقانات الاحيائية – قسم العلوم التطبيقية– الجامعة التكنولوجية

بغداد/العراق

الخلاصة :-

تم تحضير عدد من مركبات الكوينوزولين ودراسة الفعالية البايولوجية لها وقد اظهرت هذة المركبات نتائج موجبة تجاه بعض انواع البكتريا وتم تشخيص المشتقات المحضرة من مركب الكوينوزولين بواسطة تقنية الاشعة تحت الحمراء وفوق البنفسجية بالاضافة الى قياس درجات الانصهار للمركبات .