



# Synthesis of 3-Methyl-2(3-methyl-5-oxo-4, 5 dihydro 1H-pyrazol-1-yl) quinazolin-4(3H)-one and its derivatives and its antifungal and antimicrobial activity.

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## ABSTRACT

Heterocyclic compound Isothiocyanato methane (Methyl isothiocyanate) react with 2-Amino benzoic acid (Anthranilic acid) in the presence of Ethyl alcohol and triethylamine it gives an intermediate 3-methyl 2-Sulfanylquinazalin -4(3H) one as [1]. Intermediate-1 undergoes in reaction with Potassium carbonate and Methyl iodide and Dimethyl formamide (DMF) it gives 3-methyl (-2 methyl sulfanyl) quinazalin-4(3H) one as [2]. Intermediate-2 undergoes in reaction with Ethyl alcohol and hydrazine it gives 2- hydrazinyl 3-methyl quinazolin-4(3H) one as [3]. Intermediate-3 undergoes in cyclization process in the presence of EAA it gives 3-methyl-2-(3methyl-5-oxo-4,5-dihydro 1 H- pyrazol-1-yl) quinazolin -4 (3H)-one as final product and its derivative. The synthesized compounds were characterized by TLC, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and mass spectroscopy.

**Key Words:** Isothiocyanato methane, 2-Amino benzoic acid, Ethyl alcohol, Triethylamine, Potassium carbonate, Methyl iodide, DMF

## INTRODUCTION

Heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon. Such as sulphur, Oxygen or Nitrogen within a ring structure. In other word Heterocyclic compounds are cyclic compound in which the ring atoms are of carbon and some other element the atom of the other element is called the Heteroatom (Ex:- N,S or O)

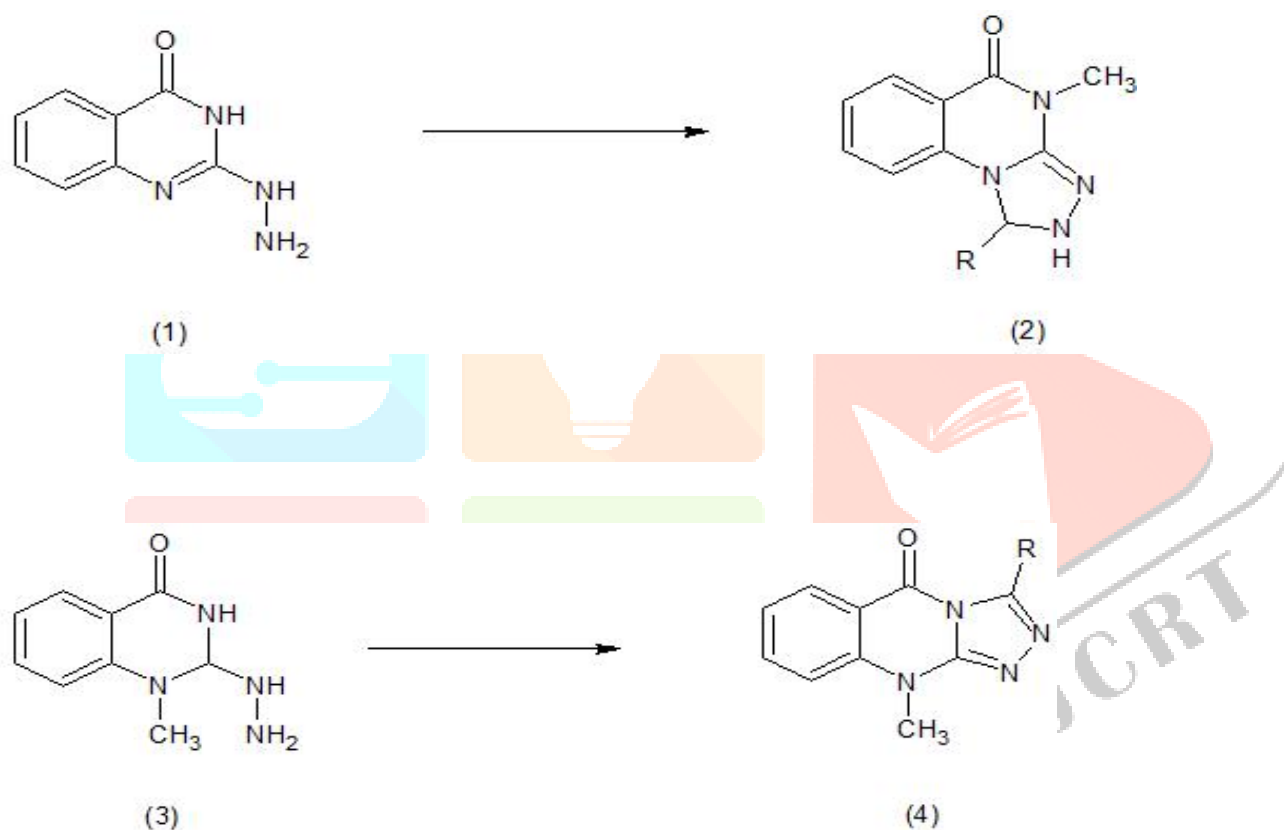
## Manufacturing process

### Brief Information about Glucosamine Plant

#### Scheme:- 1

Condensation of 2-hydrazino-4(3H)-quinazolinone (1) with bi- electrophilic reagents gives the corresponding triazoloquinazolinones 8, the structures of which were established by selective synthesis through deamination of their N-amino derivatives.

The synthesis of methyl-substituted derivatives of these angular tricyclic systems and their linear isomers was also achieved starting with 3-methyl- and 1-methyl-2-hydrazino-quinazolinone.



2,4	R
A	SH
b	H
C	Me
D	SMe

#### Scheme:- 2

The synthesis of 1-phenyl-[1,2,4]triazolo[4,3-a]quinazolin-5-one derivative is well described in the literature and followed the general methods depicted in Scheme 1. Methyl anthranilate<sup>1</sup> reacted with thiophosgene to provide the corresponding thioisocyanate<sup>2</sup> which on refluxing in toluene with benzylamine or methylamine 40% aqueous solution yielded the desired 3-substituted-2-sulfanylquinazolin-4-ones 3 and 4 via the thiourea intermediates in good yields. Nucleophilic displacement of sulfanyl group in refluxing ethanol with hydrazine hydrate in large excess yielded the desired 2-hydrazinoquinazolin-4-ones 5 and 6 with respectively, 86% and 89% yield. One of the useful methods for the

preparation of fused 1,2,4-triazoles is based on oxidative cyclization of the fused heterocyclic hydrazones with iron(III) chloride as oxidant. The hydrazones 7a-g and 8a-g were then prepared by condensation of the corresponding hydrazines with equimolaramount of benzaldehyde derivatives in refluxing methanol and the presence of a catalytic amount of acetic acid. Treatment of the hydrazones with hot ethanolic iron(III) chloride solution resulted in an in situ 1,5-electrocyclization to the angularly annelated 1,2,4-triazolo[4,3-a]quinazolin-5-ones 9a-g and 10a-g in very good yields.

7a-g  $R_1$ =benzyl

8a-g  $R_1$ =CH<sub>3</sub>

a:  $R_2, R_4$ =H;  $R_3$ =OCH<sub>3</sub>

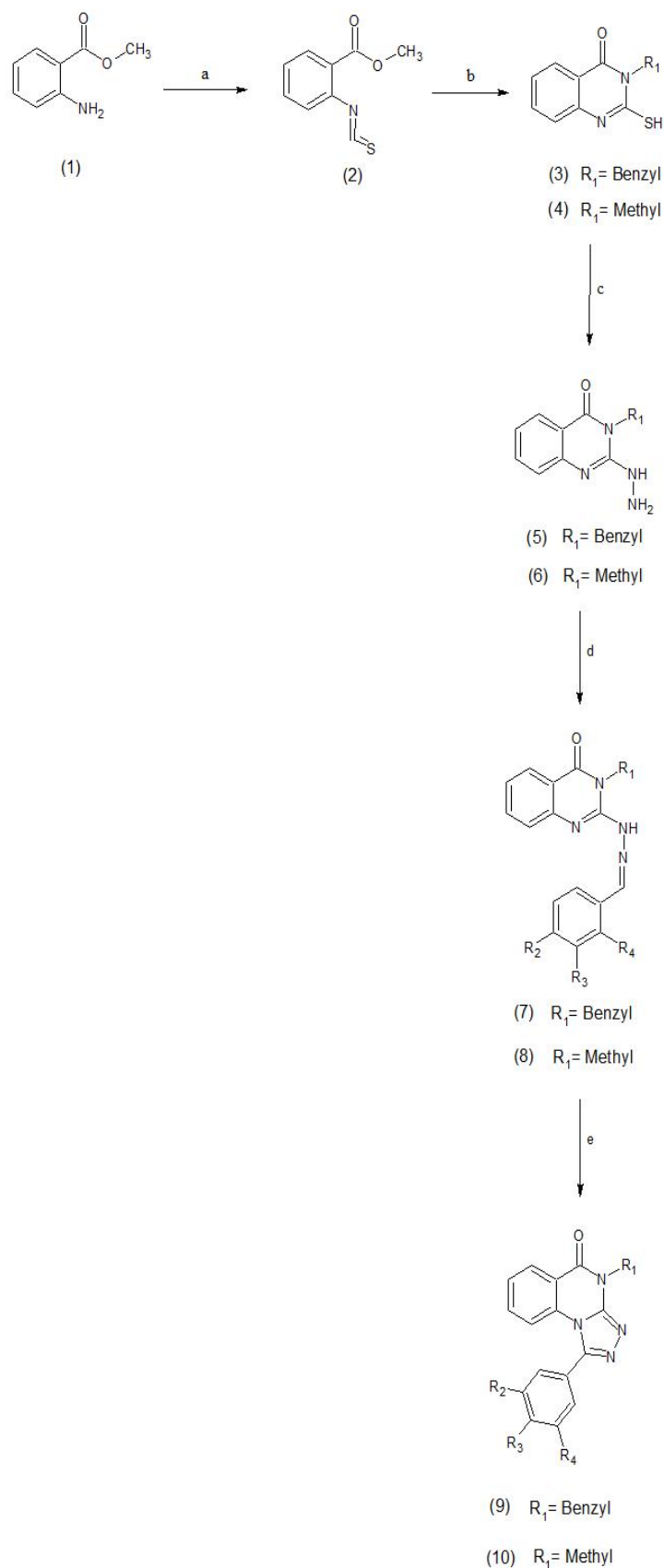
b:  $R_2$ =H;  $R_3, R_4$ =OCH<sub>3</sub>

c:  $R_2, R_3, R_4$ =OCH<sub>3</sub>

d:  $R_2$ =H;  $R_3$ =OCH<sub>3</sub>;  $R_4$ =OBn

e:  $R_2$ =H;  $R_3$ =OBn;  $R_4$ =OCH<sub>3</sub>

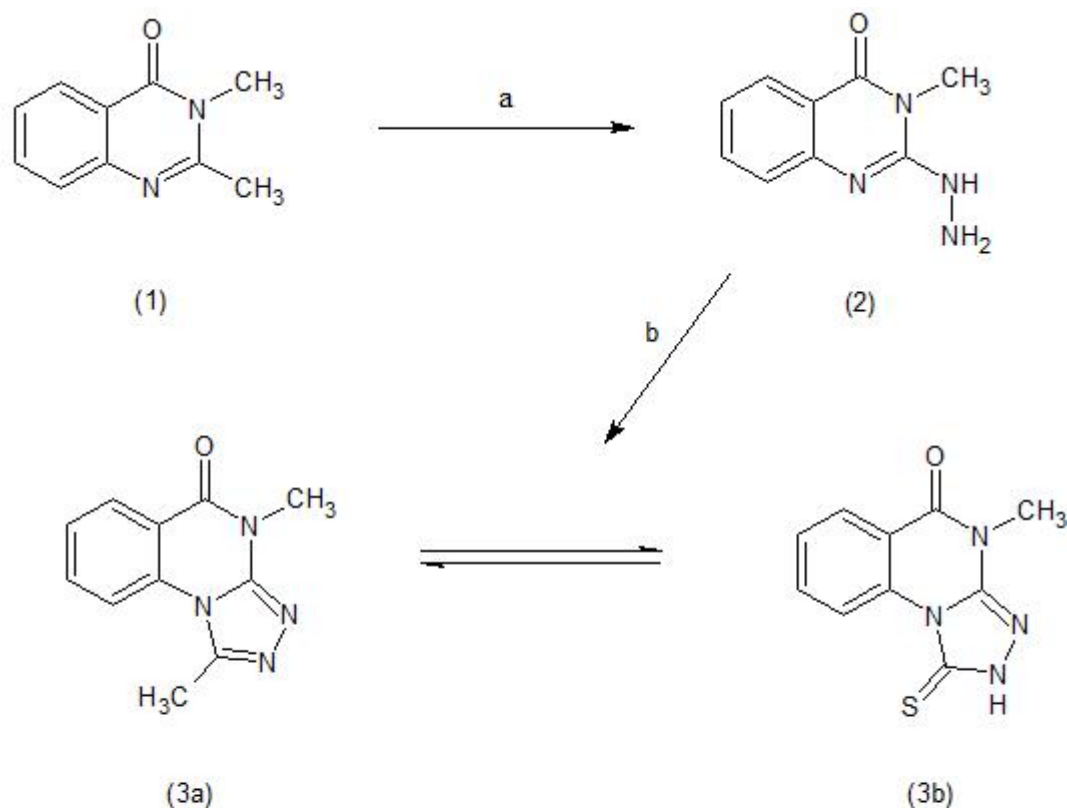




### Scheme :-3

compound 3 was prepared by a series of reactions starting from the easily available 3-methyl-2-sulfanyl-3,4-dihydro-4-quinazolinone 1. Hydrazinolysis of this starting quinazolinone afforded the hydrazine derivative 2 that subsequently reacts with carbon disulfide to give the desired product 3. The triazoloquinazoline derivative displays an interesting

tautomeric equilibrium between the thiol (3a) and thione (3b) forms. This was proven by  $^1\text{H-NMR}$  spectroscopy ( $(\text{CD}_3)_2\text{SO}$ ), which shows a mixture of these two forms in a ratio of about 1:1 thiol 3a to thione 3b forms.



a.  $\text{NH}_2\text{NH}_2$ , butanol,  $118^\circ\text{C}$ , 18h

b.  $\text{CS}_2$ , ethanol, KOH,  $70^\circ\text{C}$ , 6h

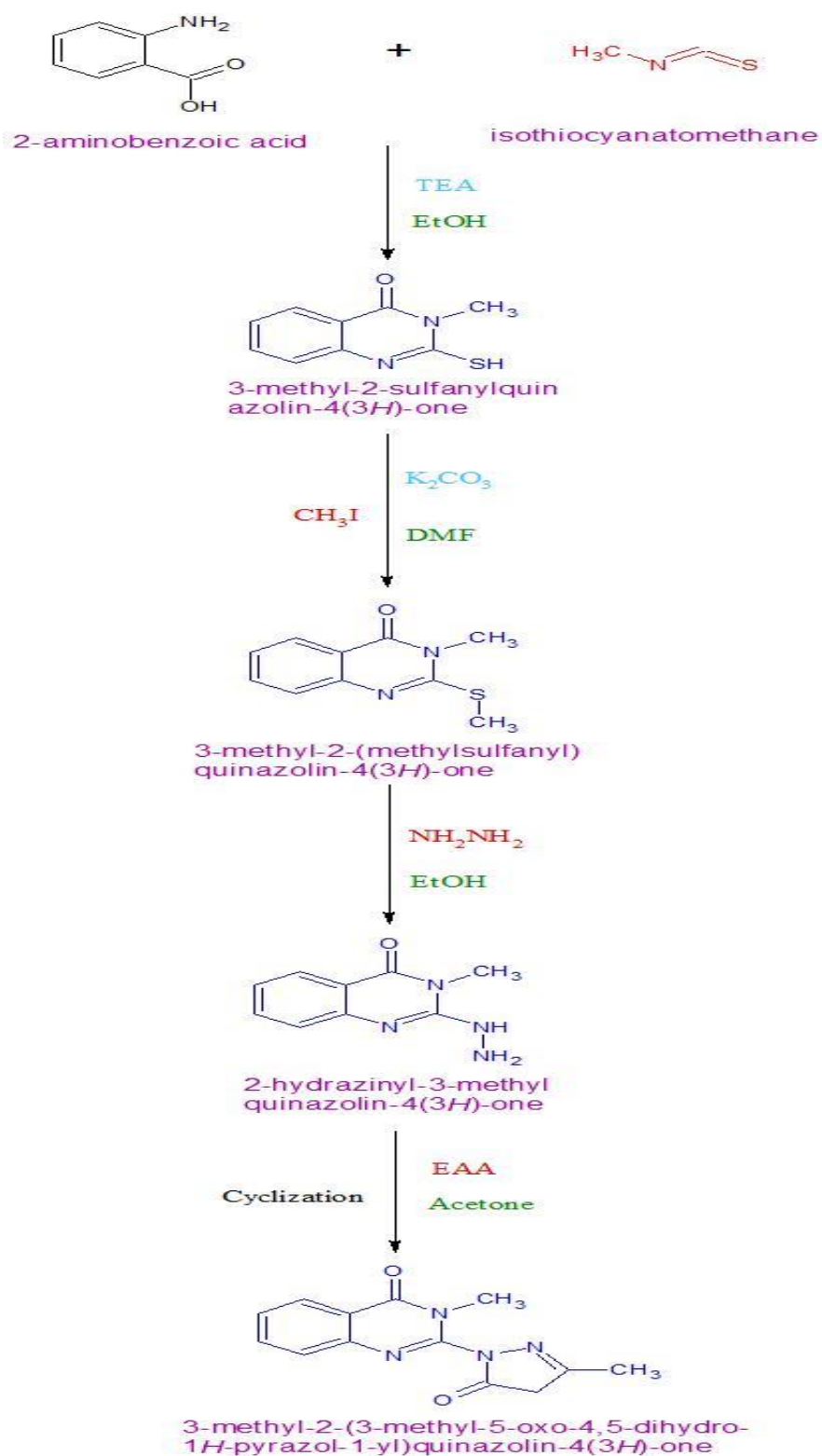
## Experiment

### Method and Material

The nomenclature of the compounds was performed using ACD Labs freeware 2012. All starting materials and other reagents were purchased from commercial suppliers and were used without any further purification unless otherwise indicated, the reaction were assayed by thin layer chromatography (TLC) and terminated as judged by the consumption of starting material Analytical thin layer chromatography (TLC) was performed on silica gel 60 F<sub>254</sub> (Merck) plates and eluted with the appropriate solvent ratio (v/v). The TLC plates were visualized by UV radiation and exposure to iodine vapour the melting point system and were recorded on optimelt automated melting point system and were uncorrected when peak multiplicities are reported the following abbreviation are used:

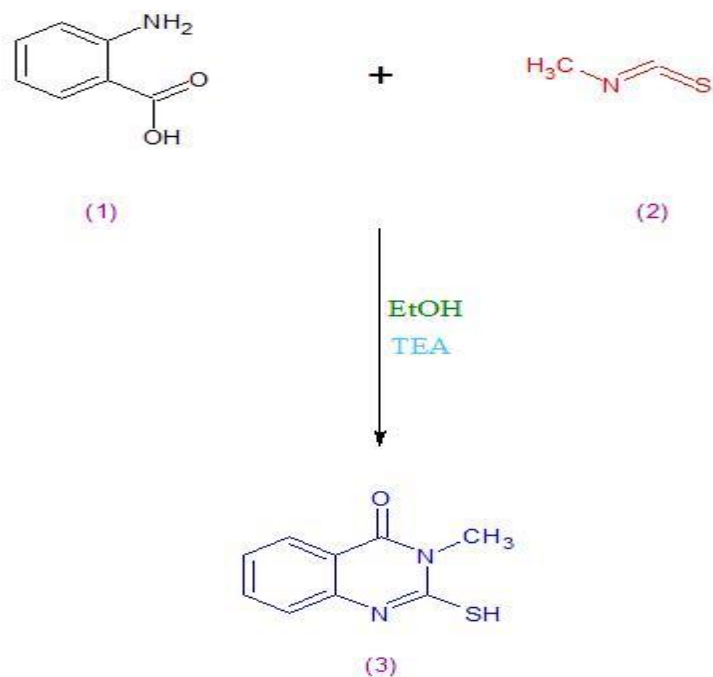
S=Singlet , d=doublet , t=triplet , q=quarted , m=multiplet , br=broadened , dd=doublet of doublets. Coupling constants are reported in (Hertz) Hz.

### 3.1 General reaction:-



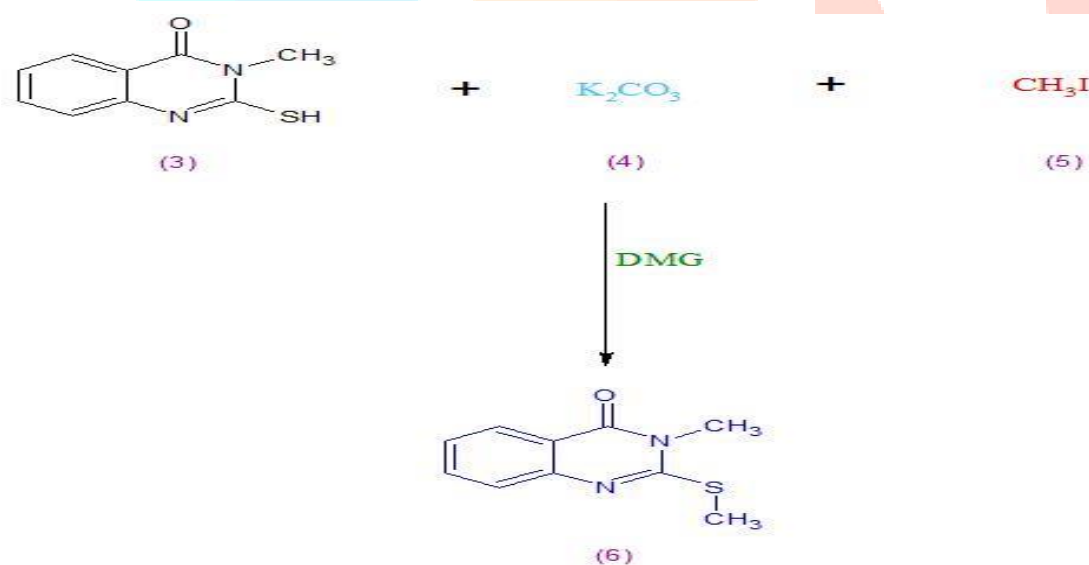
### 3.2 General procedure for the synthesis of 3-methyl-2-sulfanylquinazoline-4(3H)-one.

Anthranilic acid (5.0 gm) methyl isothiocyanate (2.66 gm) TEA {triethylamine} (10.4 ml) in 250 ml round bottom flask in ethanol (75-80 ml) the resulting mixture was stirred at room temperature for 4-5 hours till completion of reaction monitored by TLC (Ethylacetate-cyclohexane 1:3 ) as eluent. After completion of the reaction , mixture was taken in separating funnel add 75 ml ethyl acetate and shake it then add 75 ml water and again shake it. After 5-10 minutes two layers were separated. The upper layer was organic and lower layer was water layer which was desired adduct give the solid residue obtained and dried to get 3-methyl-2-sulfanylquinazoline-4(3H)-one.



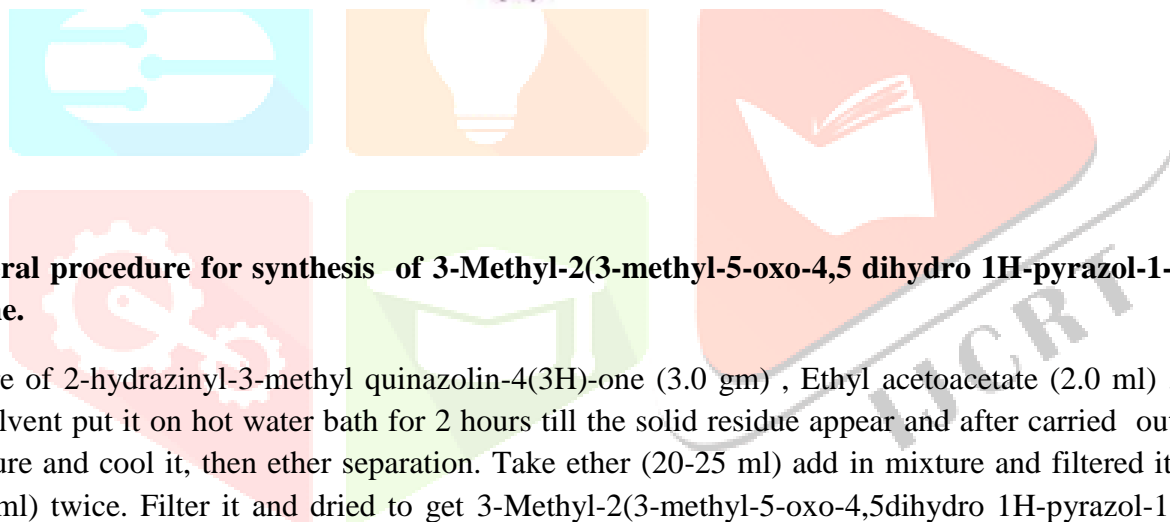
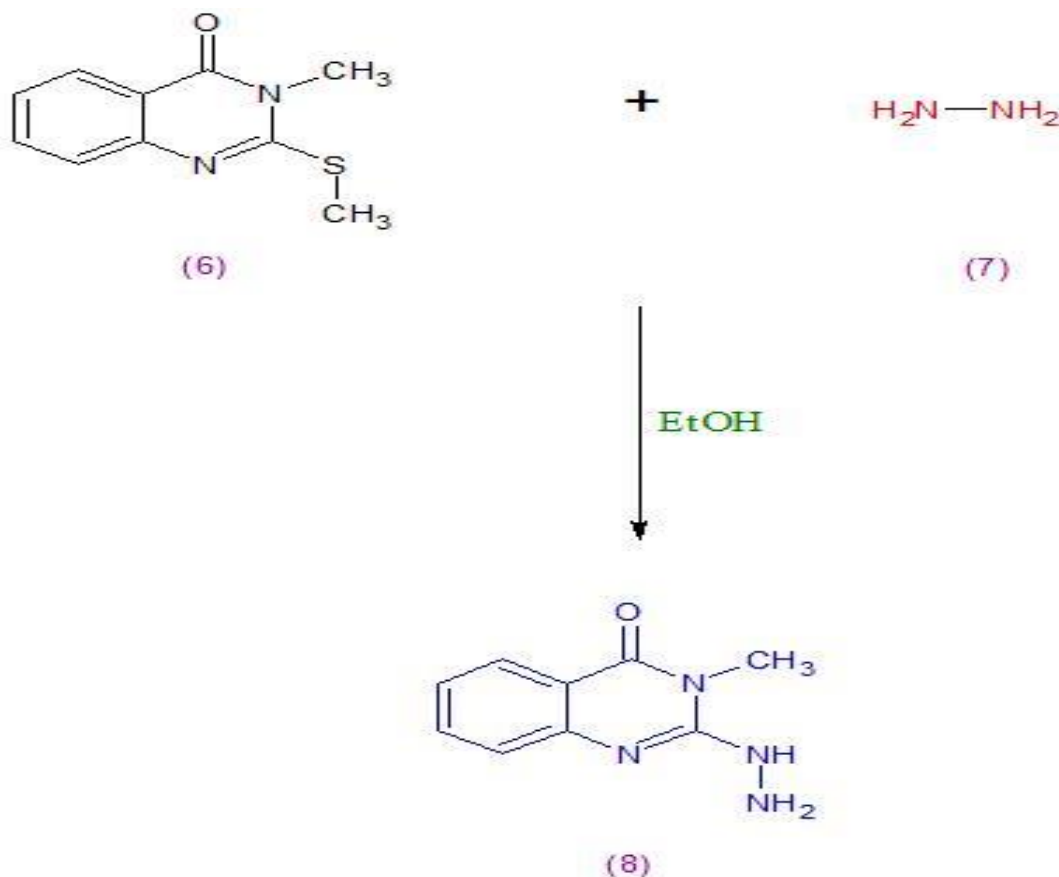
### 3.3 General procedure for the synthesis of 3-methyl-2-(methyl sulfanyl) quinazoline-4(3H)-one.

A mixture of 3-methyl-2-sulfanyl quinazolin-4(3H)-one (5.0 gm) DMF (52.8 ml) in 250 ml round bottom flask then heat this solution on a water bath. Add a  $K_2CO_3$  (7.5 gm) stir it for 15 min then methyl iodide (0.9 ml) is added in the solution and stirred at room temperature for 5-6 hours till completion of reaction monitored by TLC ( Ethyl acetate-Cyclo hexane 1:3 ). After completion of the reaction mixture were recrystalline in rectified spirit.



### 3.4 General procedure for the synthesis of 2-hydrazinyl-3-methyl quinazolin-4(3H)-one.

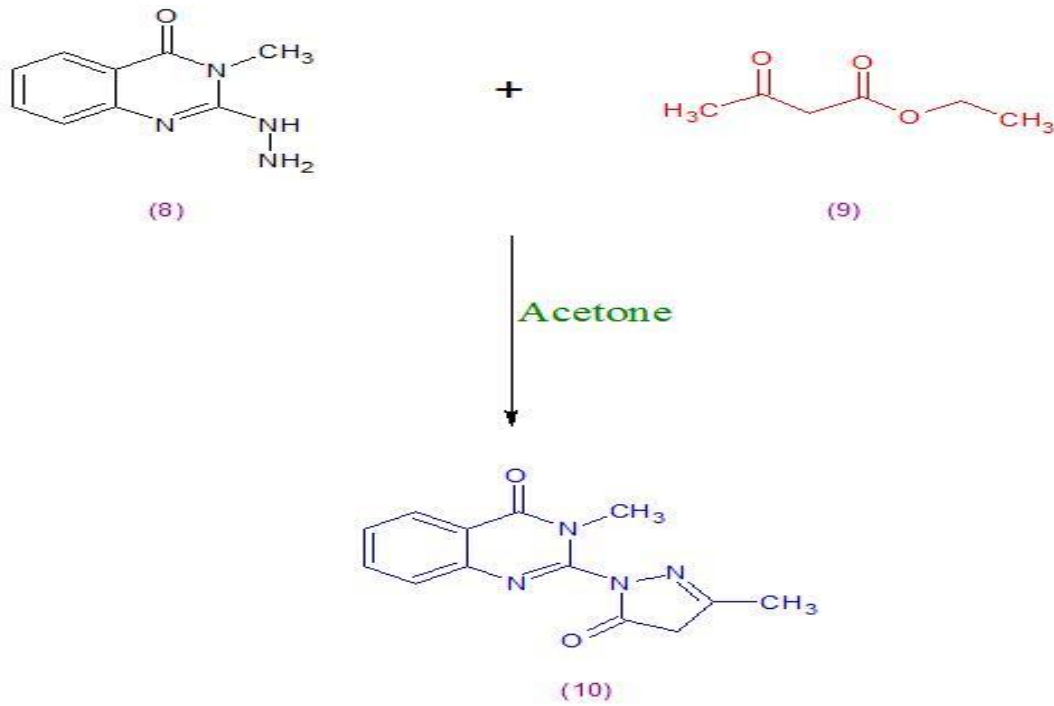
A mixture of 3-methyl-2-(methyl sulfanyl) quinazolin-4(3H)-one (4.0 gm) hydrazine hydride (6.0 ml) and ethanol (40.0 ml) in 250 ml round bottomed flask was refluxed for 10-12 hours. The process of the reaction was monitored by TLC (Ethyl acetate – Cyclohexane ) as eluent. After completion of the reaction solution put on a ice bath and the dried to get 2-hydrazinyl-3-methyl quinazolin-4(3H)-one.



### 3.5 General procedure for synthesis of 3-Methyl-2(3-methyl-5-oxo-4,5 dihydro 1H-pyrazol-1-yl) quinazolin-4(3H)-one.

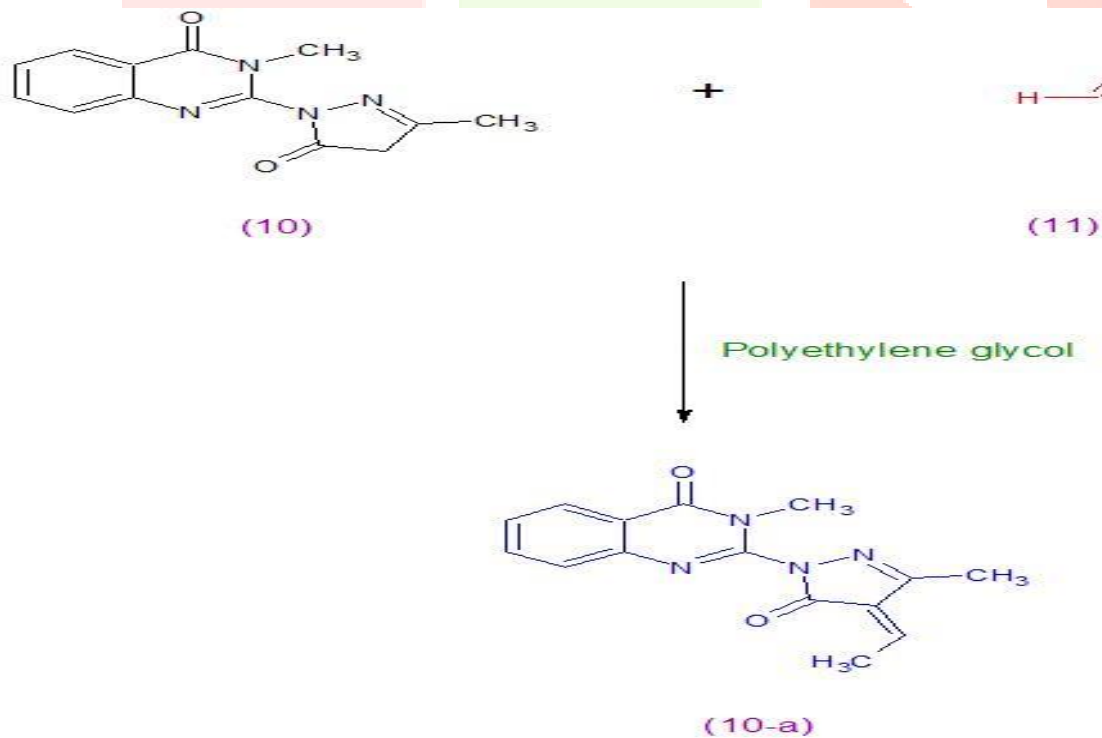
A mixture of 2-hydrazinyl-3-methyl quinazolin-4(3H)-one (3.0 gm) , Ethyl acetoacetate (2.0 ml) , Acetone (10.0 ml) as solvent put it on hot water bath for 2 hours till the solid residue appear and after carried out it on the room temperature and cool it, then ether separation. Take ether (20-25 ml) add in mixture and filtered it and wash with ether (5 ml) twice. Filter it and dried to get 3-Methyl-2(3-methyl-5-oxo-4,5dihydro 1H-pyrazol-1-yl) quinazolin-4(3H)-one and recrystalline with ethanol and water (1:1) solution.





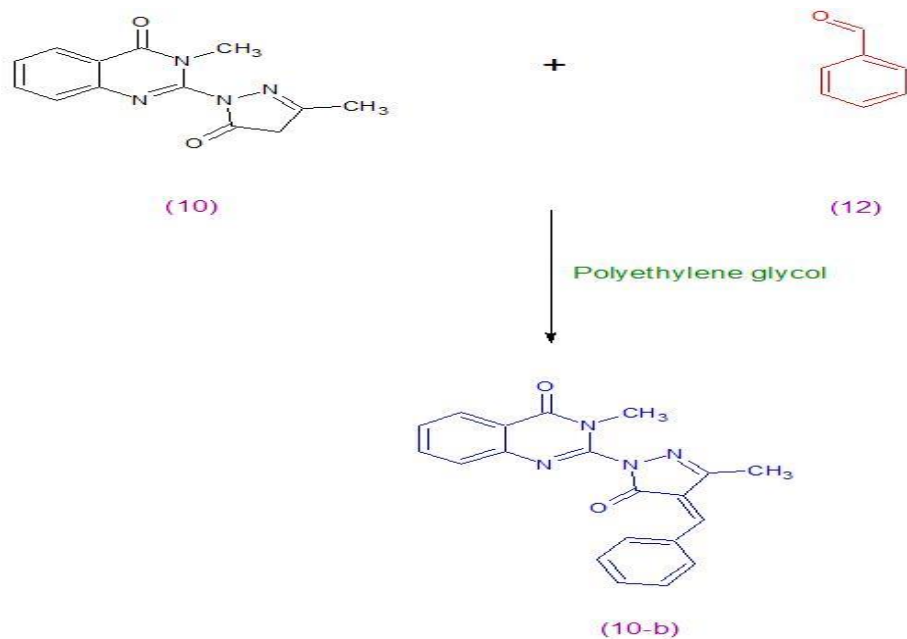
### 3.6 General procedure for synthesis of 2-[(4Z)-4-ethylidene-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-3-methylquinazolin-4(3H)-one.

A mixture of 3-Methyl-2-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl) quinazolin-4(3H)-one (2.0 gm) dissolve in poly ethylene glycol (10.0 ml), formaldehyde(0.3 ml) stir it for 2 hours. Mixture was taken to a separating funnel and add brine solution in it. After 5-10 minutes two layers were separated. The upper layer was organic and lower layer was water layer which was desired adduct give the solid residue obtained and dried to get 2-[(4Z)-4-ethylidene-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-3-methylquinazolin-4(3H)-one.



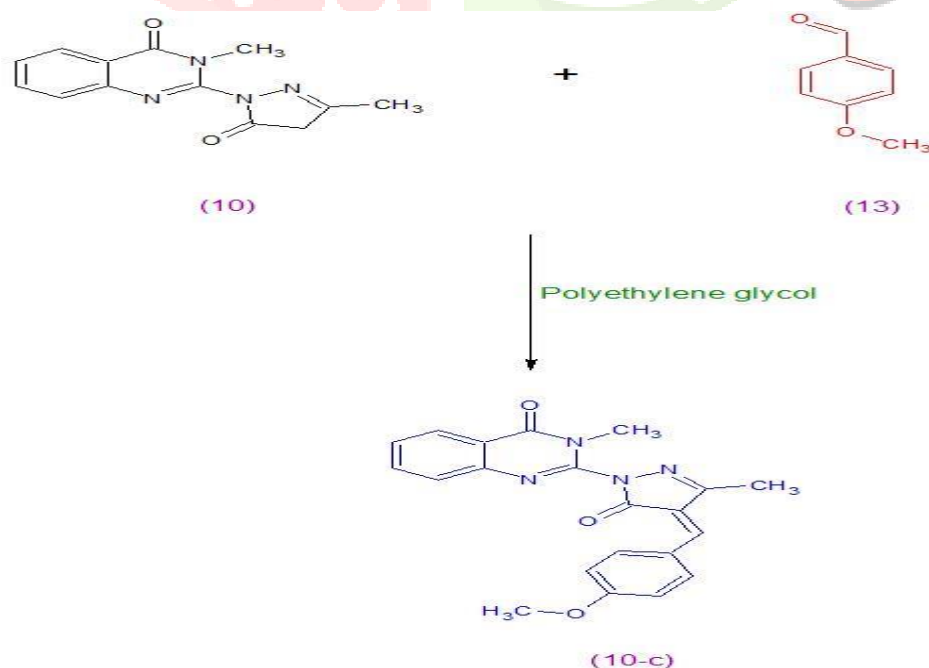
### 3.7 General procedure for synthesis of 2-[(4Z)-4-benzylidene-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-3-methyl quinazolin-4(3H)-one.

A mixture of 3-Methyl-2(3-methyl-5-oxo-4,5-dihydro 1H-pyrazol-1-yl) quinazolin-4(3H)-one (2.0 gm) dissolve in poly ethylene glycol (10.0 ml), benzaldehyde(0.8 ml) stir it for 2 hours. Mixture was taken to a separating funnel and add brine solution in it. After 5-10 minutes two layers were separated. The upper layer was organic and lower layer was water layer which was desired adduct give the solid residue obtained and dried to get 2-[(4Z)-4-benzylidene-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-3-methylquinazolin-4(3H)-one.



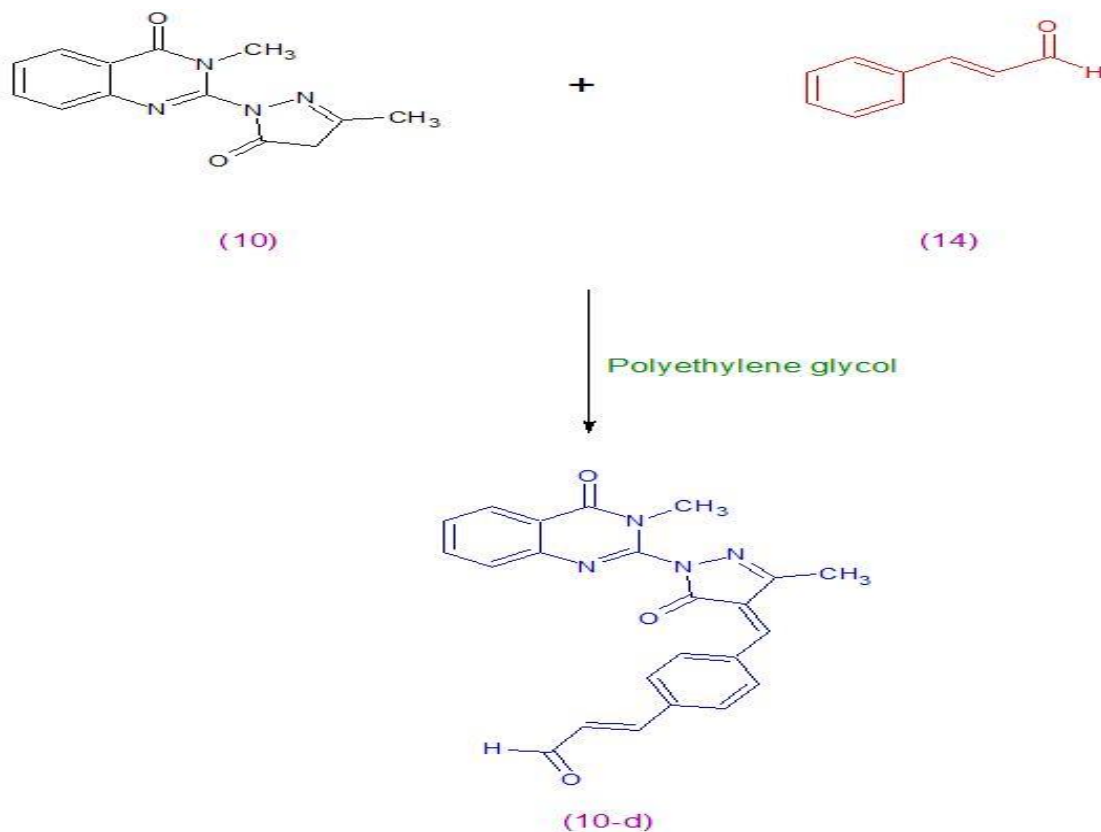
### 3.8 General procedure for synthesis of 2-[(4Z)-4-(4-methoxybenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-3-methylquinazolin-4(3H)-one.

A mixture of 3-Methyl-2(3-methyl-5-oxo-4,5-dihydro 1H-pyrazol-1-yl) quinazolin-4(3H)-one (2.0 gm) dissolve in poly ethylene glycol (10.0 ml), anisaldehyde (1.0 ml) stir it for 2 hours. Mixture was taken to a separating funnel and add brine solution in it. After 5-10 minutes two layers were separated. The upper layer was organic and lower layer was water layer which was desired adduct give the solid residue obtained and dried to get 2-[(4Z)-4-(4-methoxybenzylidene)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-3-methylquinazolin-4(3H)-one.



### 3.9 General procedure for synthesis of (2E)-3-(4-((Z)-[3-methyl-1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]methyl)phenyl)prop-2-enal.

A mixture of 3-Methyl-2(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)quinazolin-4(3H)-one (2.0 gm) dissolve in poly ethylene glycol (10.0 ml), cinnamaldehyde (1.0 ml) stir it for 2 hours. Mixture was taken to a separating funnel and add brine solution in it. After 5-10 minutes two layers were separated. The upper layer was organic and lower layer was water layer which was desired adduct give the solid residue obtained and dried to get (2E)-3-(4-((Z)-[3-methyl-1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]methyl)phenyl)prop-2-enal.



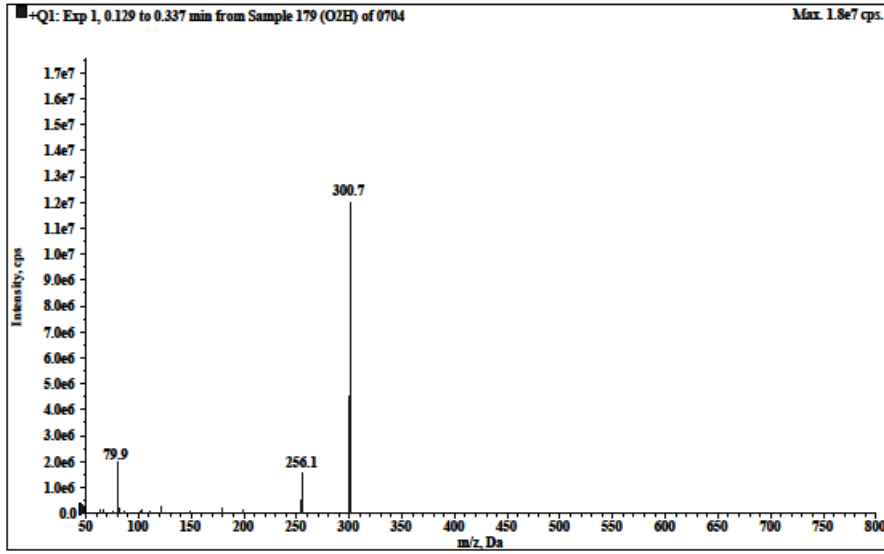
#### Result and Discussion

Derivative of formaldehyde which give a derivative product 2-[(4Z)-4-ethylidene-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]-3-methylquinazolin-4(3H)-one.



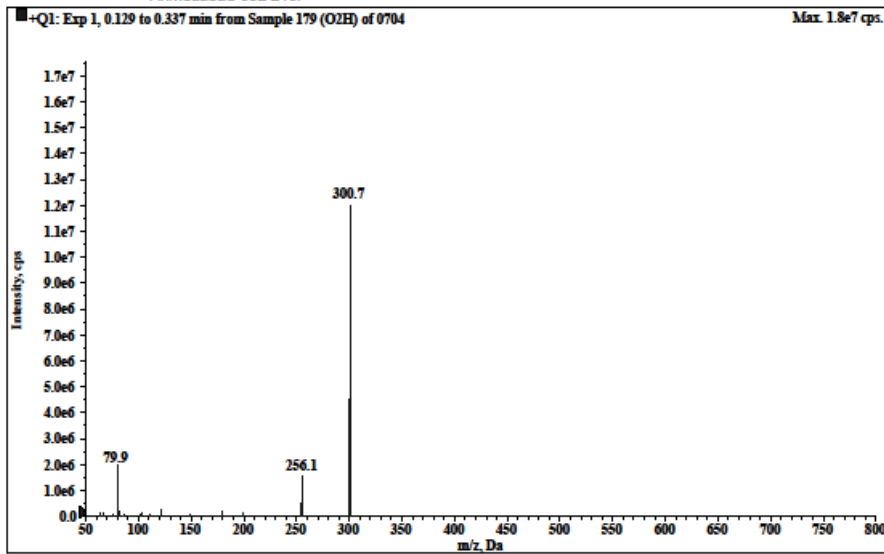
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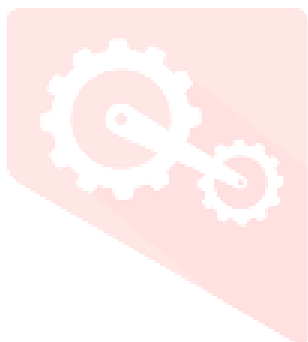
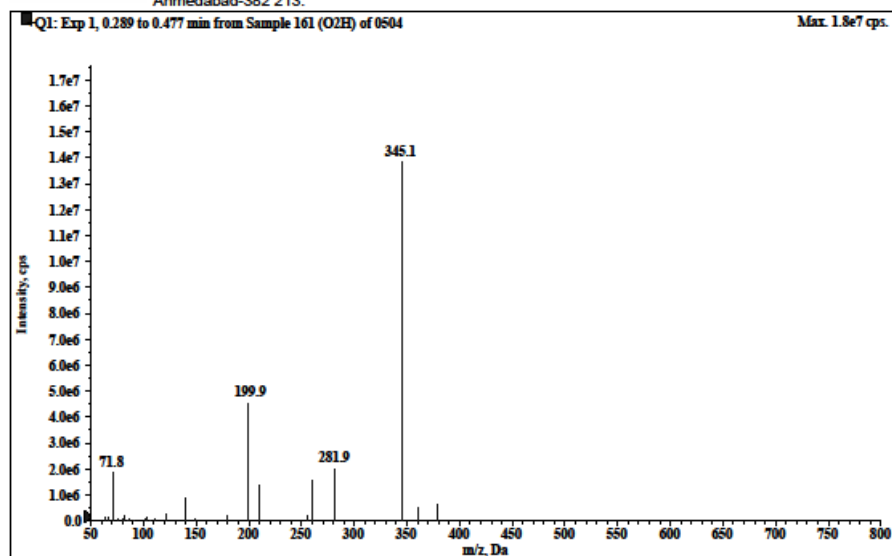


Derivative of benzaldehyde which give product 2-[(4Z)-4-benzylidene-3-methyl-5-oxo-4,5-dihydro1H-pyrazol-1-yl]-3-methylquinazolin-4(3H)-one.



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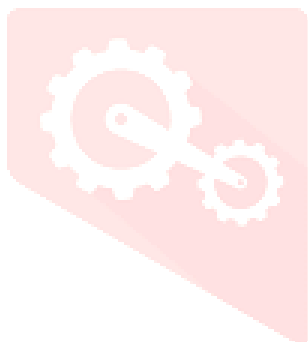
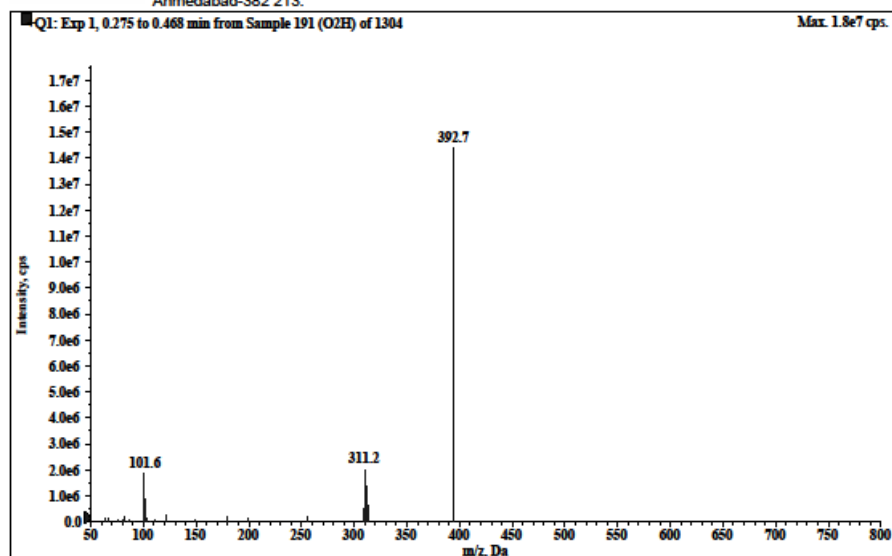


Derivative of anisaldehyde which give (2E)-3-(4-((Z)-[3-methyl-1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl) -5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]methyl}phenyl)prop-2-enal.



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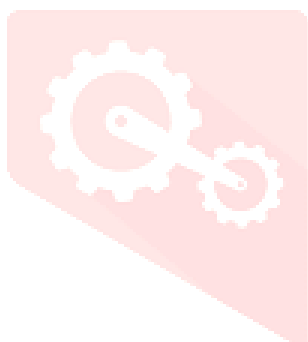
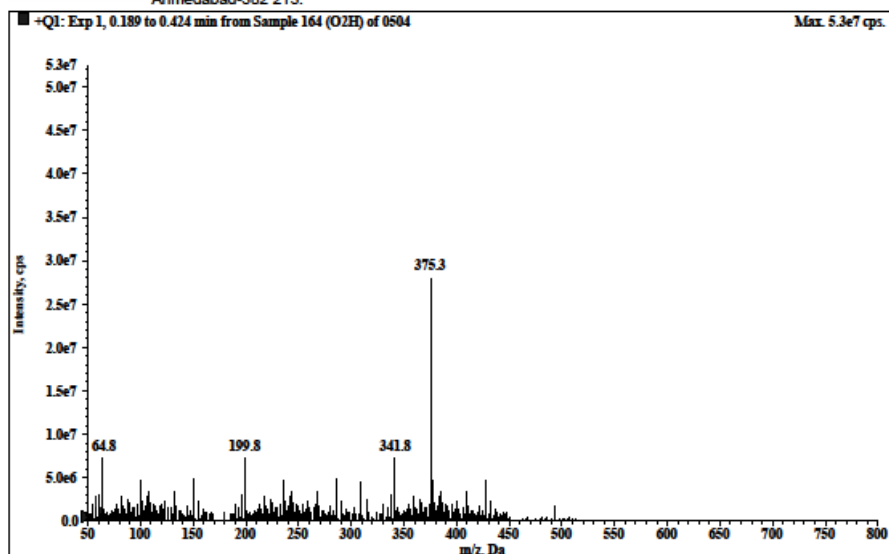


Derivative of cinnamaldehyde which give (2E)-3-(4-((Z)-[3-methyl-1-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene]methyl}phenyl)prop-2-enal



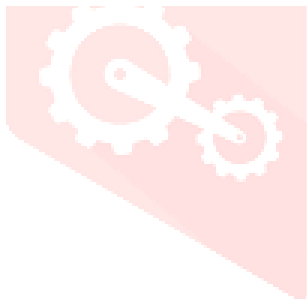
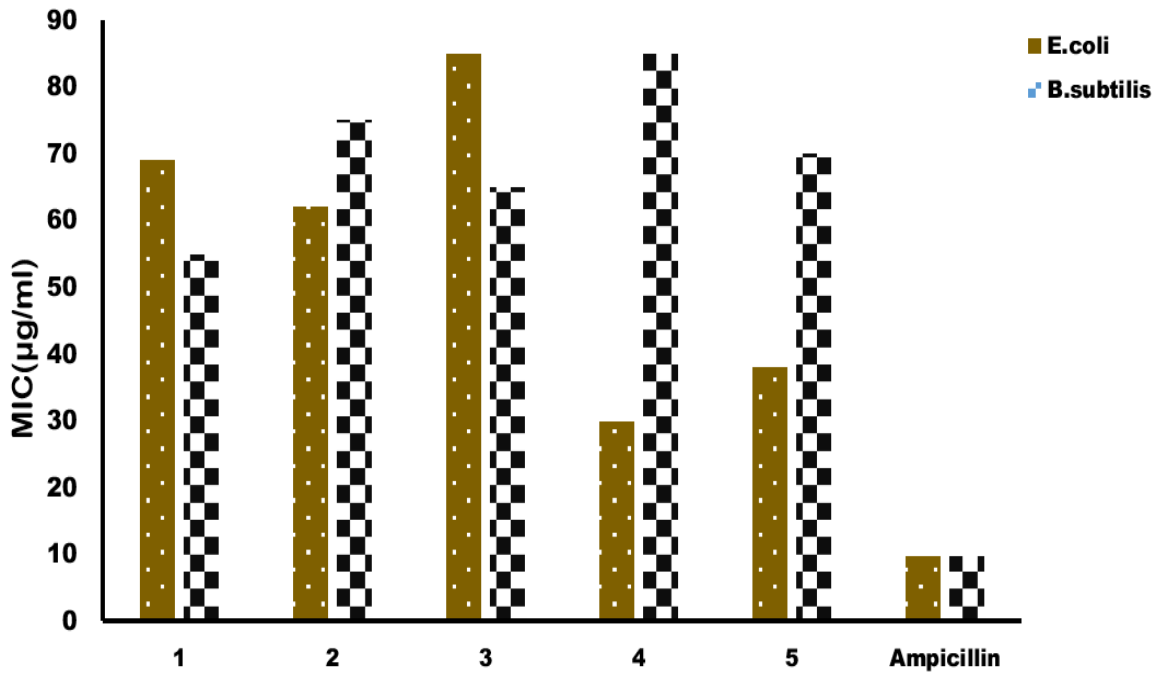
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### Antimicrobial activity of 3-Methyl-2(3-methyl-5-oxo-4,5dihydro 1H-pyrazol-1-yl) quinazolin-4(3H)-one.

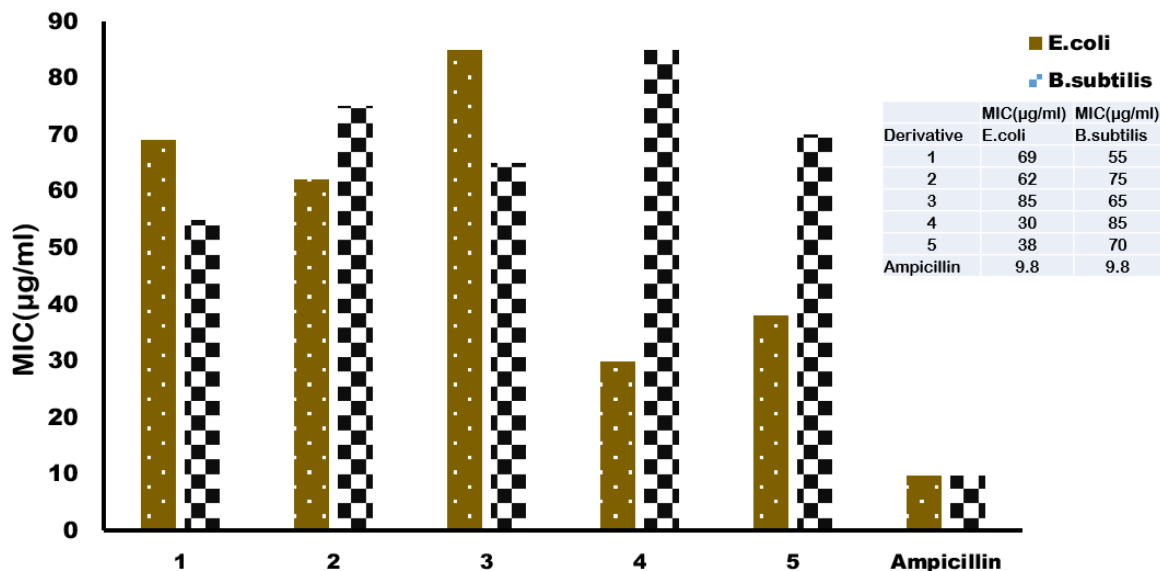
#### Potential antimicrobial activity against gram-negative bacteria





## Antimicrobial activity of 3-Methyl-2(3-methyl-5-oxo-4,5dihydro 1H-pyrazol-1-yl) quinazolin-4(3H)-one.

### Potential antimicrobial activity against gram-negative bacteria



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