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Research Article

SYNTHESIS AND THEORETICAL STUDY OF NEW QUINAZOLINONE DERIVATIVES CONTAINING VARIOUS HETEROCYCLIC MOIETIES

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ABSTRACT

In this work, quinazolinone derivatives were prepared, characterized by IR, UV, HNMR spectroscopy. Theoretically these compounds were studied using Hartree-Fock method and 3-21G basis set, where it was found HOMO-LUMO and thermodynamic functions (ΔH^{o}_{f}, ΔG^{o}_{f} and ΔS^{o}_{f}) calculations, which found from values of these functions that the reactions of quinazolinone derivatives synthesis were exothermic reaction.

KEYWORDS: Quinazolinone Derivatives, IR, UV Spectroscopy, theoretical study and Hartree-Fock method

INTRODUCTION

Quinazolinone is an interesting and important aromatic heterocyclic system[1]. Quinazolinone have been frequently used in medicine because of their wide range of biological activities[2]. They are considered to be a potent structure for drug Developments[3] Different quinazolinone derivatives have been reported for their antibacterial, antifungal[4], anticancer[5], anti HIV, anti-inflammatory, CNS depressants[6] and anti tubercular activities[7,8].

MATERIALS AND METHODS

All of the reagents are commercially available in the (Aldrich Co.). Melting point was recorded by electric thermal melting point apparatus. FT-IR measurements have been recorded through the model Shimadzu FT-IR-8400S., UV. Spectra was measured by CARY 100, VARIAN Co. Model and H^1 NMR spectra using Ultra Shield Bruker laboratory model in the 300 MHz using DMSO-D6 as a solvent and used of TMS, according to internal standards.

Synthesis of 2-Mercapto -3-(pyridine-2-yl)quinazolin-4(3H)-one (1)

Carbon disulfide (12ml) was added drop wise to an ice cold solution of potassium hydroxide (0.015 mol) in absolute ethanol (25 ml) containing solution of anthranilic (0.01mol) and (0.01mol) 2-amino pyridine .The mixture refluxed for 8 hours then poured into ice-water. The solid was filtered washed with water and re crystallized from ethanol. Yield: 78%. M.p. 180-182°C.

Synthesis of 2- Hydrazinenyl-3-(pyridine-2-yl)quinazolin-4(3H)-one (2)

A mixture of ethyl ester (0.01mol) and hydrazine hydrate 99 % (0.01mol) in absolute ethanol was heated under reflux for 8hrs The excess of ethanol was distilled-off to a possible extent and cooled. The resultant solid was separated by filtration and dried. It was purified by re crystallization from ethanol. 85%. M.p. 199-201°C.

Synthesis of 2-(2-(4-bromo benzylidine)hydrazinyl)-3-(pyridine-2-yl)quinazolin-4(3H)-one (3)

A mixture of hydrazides (2) (0.0043mol), (0.0043mole)of the 4-Bromobezaldehydeand 0.1 ml of glacial acetic acid in (50ml) methanol was refluxed for 8 hrs. The formed precipitate was filtered, dried and purification from chloroform Yield: 73%. M.p.: 210--212°C.

Synthesis of 2-((2-(4-bromo phenyl)-3-chloro-4-oxoazetidin-1-yl)amino)3-(pyridine-2-yl)quinazolin-4(3H)-one (4)

A mixture of Schiff base(3) (0.01 mol) and tri ethyl amine (0.02 mol) was dissolved in Dioxane (20 ml). chloro acetyl chloride (0.02 mol) was added in portion wise with vigorous shaking at room temperature for 30 min. The reaction mixture was heated under reflux for 5h and the content was kept at room temperature for 24 h and poured into ice-cold water. The product obtained was filtered, washed several times with water. Yield: 78%. M.p.: 226-228°C.

Synthesis of 2-(4-bromo phenyl)-3-((4-oxo-3-(pyridine-2-yl)-3,4-dihydroquinazolinyl)amino)thiazolidin-4-one (5)

A mixture of Compound (3) (0.001mol) was solved in 30mL chloroform with ZnCl2 (0.01g) and (0.005mol) of thio glycolic acid was added to the mixture, the mixture was refluxed for 10h. The reaction completion was monitored by thin layer chromatography (TLC) using ethyl acetate : hexane system (3:7). The solvent was removed under reduced pressure, residue treated by solution of 10% NaHCO3 to removed excess of mercapto

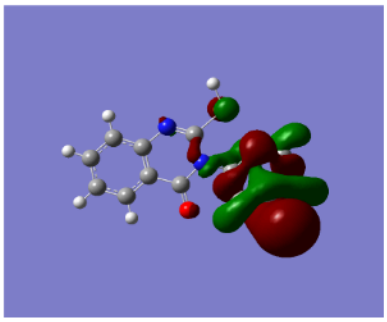
acetic acid, washed with water, dried and re crystallization from acetone. Yield: 70%.M.p. 182-184°C.

Antimicrobial Activity

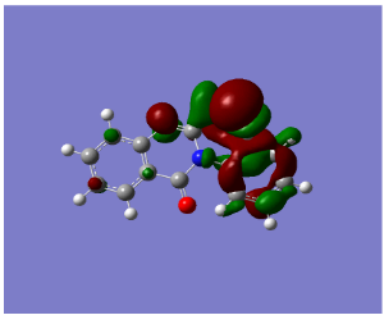
The antimicrobial activity of the quinazolinone derivatives were tested by the agar disc-diffusion method against two Gram positive *Staphylococcus aureus and Streptococcus pyogenes* and two gram negative bacteria *E. Coli ,Klebsielllaspp micro organisms* and fungal strains namely *Candida albicans*. Dimethyl sulfoxide DMSO was used as a control and as solvent .The test was performed at 100mg/mL concentration. The bacteria and fungi were carried out in agar and potato dextrose agar medium and these plates were incubated for 24 h for bacteria and 48h for fungi at 37 °C.

ComputationalDetails

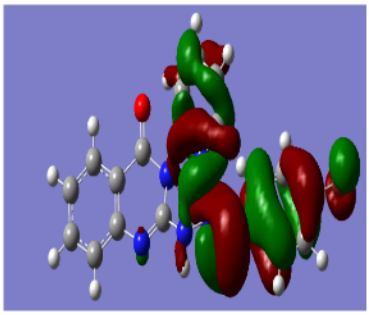
Hartree –Fock method were performed with the Gaussian 09 series of programs. The total energy of the prepared compounds was calculated at Basis Set 3-21G. by this method (IR, UV) spectrum and thermodynamic functions (ΔH^{o}_{f} , ΔG^{o}_{f} and ΔS^{o}_{f}) were studied[9]. Figure1 shows the HOMO and LUMO for the compounds:



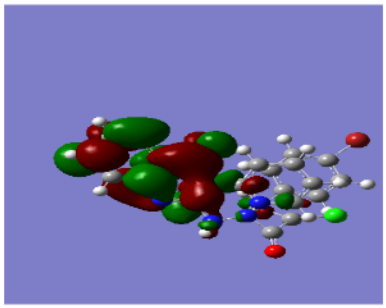
Compound 1



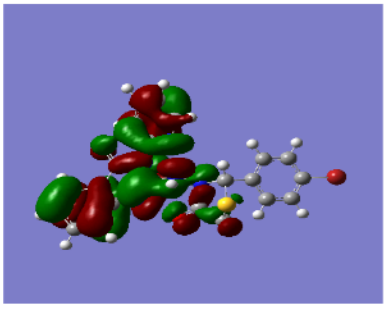
Compound 2



Compound 3



Compound 4

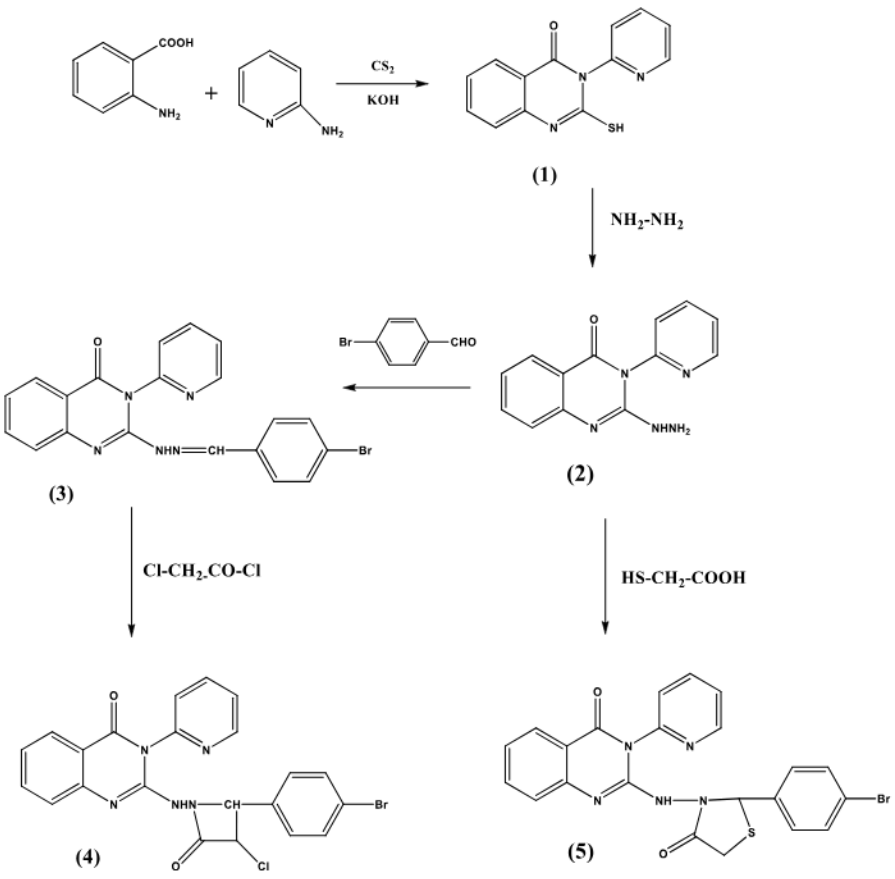


Compound 5

Figure 1: HOMO-LUMO Categories of the prepared compounds

RESULTS AND DISCUSSION

The new quinazolinone derivatives were prepared following the reaction sequences depicted in Scheme 1.



Scheme 1

FTIR Spectra

The 2-hydrazineyl-3-(pyridin-2-yl)quinazolin-4(3H)-one (2) ws prepared by refluxing of compound 1 with hydrazine hydrate in absolute ethanol for 8 h. The FTIR spectrum indicated the appearance two bands in the region (3363-3176) cm^{-1} which could be attributed to asymmetric and symmetric stretching vibration of $NH_2$and NH. Condensation of the compound (2) with *p*-bromobenzaldehyde in absolute ethanol afforded the Schiff base (3). The formation of Schiff base was indicated by the presence in their FTIR spectra of azomethine (CH=N) stretching band at (1616) cm^{-1}, combined with the disappearance of the NH_2 stretching band. Furthermore, the generation of azetidinyl derivative (4) by the reaction of Schiff base (3) with Et3N and chloroacetyl chloride ($C_2H_2OCl_2$) in dioxone .The FT-IR spectrum indicatedthe appearance of band at 1728cm^{-1} (C=O) due to β-lactam with disappearance band of imine (N=CH) in the region 1616 cm^{-1}. Cyclization1 of schiff base (3) with mercapto acetic acid in the presence of chloroform as solvant1afforded thiazolidenone (5).The structures of 1compound(5)was confirmed by the presence of1 carbonyl 1stretching 1band at (1705) cm^{-1}due to thiazolidinone ring which was the characteristic evidence for success of cyclization. Figures 2, 3 and table 1 showed the FTIR spectrum of the compounds 3 and
5.

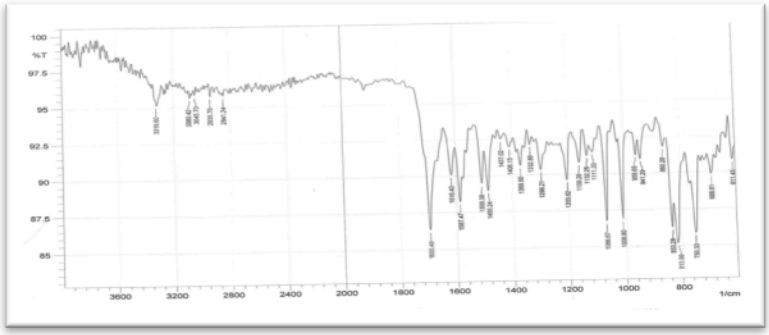


Figure2: FTIR Spectra of compound 3

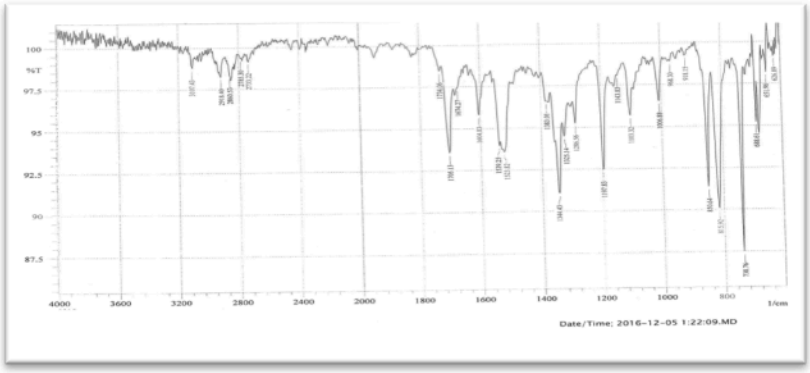


Figure3: FTIR Spectra of compound 5

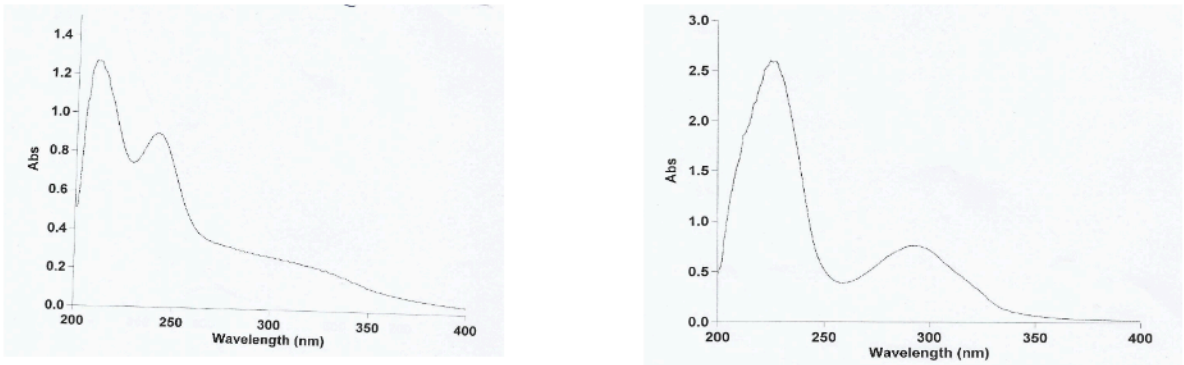
Table1: Experimental and Theoretical values of FTIR Spectrum bands of prepared compounds

Compound	υ (C=O)	υ(CH=N)	υ(N-H)	υ(C=S)
Comp.1	1685 (1693)H	---------	3367 (3381)H	1610 (1607)H
Comp.2	1656 (1670)H	----------	3363-3176 (3367)H	---------
Comp.3	1690 (1694)H	1620 (1616)H	3210 (3348)H	---------
Comp.4	1687(amide) (1640)H 1728(lactam) (1727)H	---------	3340 (3321)H	---------
Comp.5	1725 (1720)H	---------	3328 (3304)H	---------

H: Hartree-Fock

UV. Spectra

The UV spectra of the prepared compounds showed in figure 4 and table 2:



1 5

Figure4: UV Spectra of the compounds 1 and 5

Table2: Experimental and Theoretical bands of UV Spectrum of prepared compounds

Compound	Band I	Band II
Comp. 1	241 (243)H	209 (211)H
Comp.2	247 (245)H	206 (215)H
Comp.3	292 (301)H	225 (223)H
Comp.4	290 (309)H	232 (227)H
Comp.5	293 (303)H	227 (218)H

H: Hartree-Fock

H^1NMR Spectra

H^1NMR spectrum of compound 1 (δ, ppm): 9.23(s, 1H, NH), 8.46-6 .45 (m, 8H, Ar-H). compound (2) exhibited singlent signal at 3.5ppm and at 9.38 ppm was assigned to NH proton, signal at 5.71 ppm was attributed protons of NH2,aromatic protons were appeared at 8.0-7.05ppm. The ^{1}HNMR of derivative (3) showed singlet signal at8.7ppm due to NH proton ,while aromatic protons and proton of CH=N appears as multiple signals at 8.1-6.2 ppm . For compound 4, H^1NMR(300 MHz, δ, ppm , DMSO-d6): 9.45 (s, 1H, NH), 8.45-6.52 (m, 8H, Ar-H), 5.5 -5.0 (dd, 2H, CH). Compound 5 appears 8.78 (s, 1H, NH), 8.53-6.46 (m, 8H, Ar- H), 5.40 (s, 1H, CH-N), 3.83 (s, 2H, CH_2). Figures 5 and 6 show the H^1NMR spectrum of compounds 2 and
3.

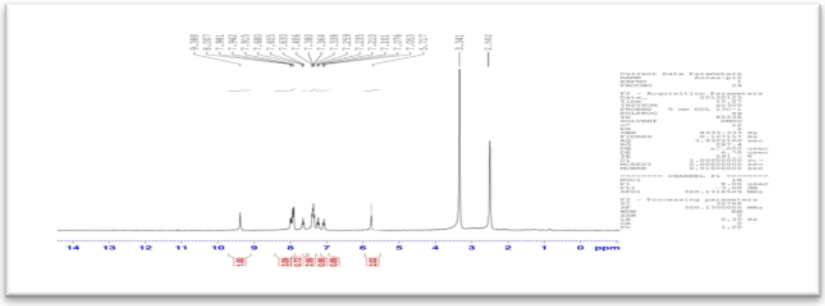


Figure 5: H^1NMR Spectra of compound 2

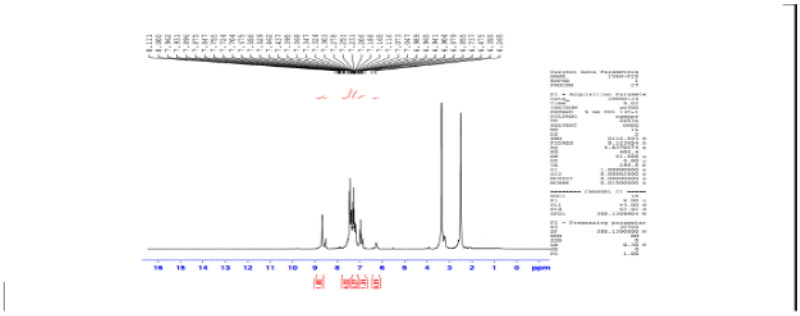


Figure 6: H^1NMR Spectra of compound 3

***A*ntimicrobial Activity**

According to table 3 compound 1 showed that it had no effect of inhibition on *Staphylococcus aureus*, while compound 2 showed that it had no effect of inhibition on *Klebsielllasppmicroorganisms*. Compounds 3, 4 and 5 showed inhibition for all kinds of bacteria higher than other compounds.

Table3: Antimicrobial Evaluation of prepared compounds

Heterocyclic Derivative	inhibition zone (mm) at 100 mg/mL				
	Grampositive		Gram negative		Fungi
	S. aureus	*S.epidermidis*	*E.coli*	*Klebsiellaspp*	*C.albicanus*
Comp.1	-	14	16	15	15
Comp.2	15	12	16	-	15
Comp.3	16	15	14	11	18
Comp.4	18	13	12	20	15
Comp.5	20	19	17	22	19

Thermodynamic Properties

Thermodynamic properties of the prepared compounds were calculated theoretically using Hartree-Fock method by Gaussian 09 program. Table 4 shows the thermodynamic functions (ΔH^o_f, ΔG^o_f and ΔS^o_f) of these compounds:

Table4: Thermodynamic properties of prepared compounds

Comp.	ΔH^o_f (kcal/mol)	ΔG^o_f (kcal/mol)	ΔS^o_f (cal/mol.K^{-1})
Comp.1	-223546.494	-223528.924	-58.959
Comp.2	-840.443	-840.491	-0.161
Comp.3	-3665.912	-3665.974	-0.208
Comp.4	-4268.994	-4269.051	-0.191
Comp.5	-4211.036	-4211.101	-0.218

Above table showed that the reactions of compounds synthesis were exothermic reactions.

CONCLUSIONS

we concluded from the comparison between the experimental and theoretical results using HF method with basis set 3-21G that there is a simple difference between them the reason is that these programs operate in standard conditions and in a gas situation. From the study of antimicrobial activity of quinazolineone derivatives on the different kinds of bacteria showed that these compounds had significant effect in the inhibition of these bacteria. The values of thermodynamic function (negative enthalpy, negative entropy and negative free energy) showed that the synthesis reactions of quinazolineone derivatives from compound 1 to compound 5 were (exothermic reactions).

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