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Experimental and Theoretical Study on One-pot, Synthesis of Some 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones Derivatives (HHQs) using Nano K_3AlF_6

Masoumeh Mehrabi[1,2], Asadollah Farhadi[*2,3], Alireza Kiassat[2,4]

[1]*Department of Chemistry, Khuzestan Science and Research Branch, Islamic Azad University, Ahvaz, Iran*

[2]*Department of chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran*

[3]*Petroleum University of Technology, Faculty of Science, Ahvaz, Iran*

[4]*Chemistry Department, College of Science, Shahid Chamran University, Ahvaz, Iran*

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Abstract

A one-pot three-component procedure has been developed for the synthesis of 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones derivatives (HHQs) using urea, 1,3-cyclohexadione and aryl aldehydes in acetonitrile at room temperature and at the presence of catalytic amounts of Nano K_3AlF_6. Synthesis of these new Biginelli-type products (HHQs) requires a very mild reaction conditions. This reaction may be considered as a complementary to the classical Biginelli synthesis. A mechanism was proposed for this reaction. The zeta potential changes of K_3AlF_6, K_3AlF_6@benzaldehyde, K_3AlF_6@1,3-cyclohexadiones and K_3AlF_6@urea in acetonitrile related to this mechanism were reported. These products were characterized by FT-IR, UV/Vis, Mass, ^{1}H NMR and ^{13}C NMR spectra. Nano catalyst was also characterized by FT-IR, XRD, XRF, SEM and TEM methods. This catalyst is easily prepared and also is stable, reusable and efficiently used under reaction conditions. The structures of synthesized molecules were studied using a density functional theoretical (DFT) method and second order perturbation theory analysis of Fock matrix with NBO basis. Furthermore, the solvation Gibbs energies and the electronic properties of these compounds in water and ethanol were studied.

Keywords*:* 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (HHQs), Zeta Potential, 1,3-cyclohexadione, Nano K_3AlF_6, DFT, Solvation Gibbs energies

*Corresponding author:Asadollah Farhadi,Department of chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz Iran. Petroleum University of Technology, Faculty of Science, Ahvaz, Iran. Email: farhadichem@put.ac.ir.

Introduction

4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones derivatives (HHQs)have occupied an important position in natural and synthetic organic chemistry. Because these compounds have properties like biological activities such as antibacterial, antiviral, antihypertensive and calcium channel blockers. [1] Also, some of HHQs are highly important for creating structural diversity to produce a drug like molecules for biological screening. [2]HHQs compounds are structurally similar to those of 3,4-dihydropyrimidinones (DHPMs). For the first time, P. Biginelli was reported synthesis of some 3,4-dihydropyrimidinones (DHPMs) in 1893. [3] Biginelli-type products are highly regarded for their pharmacological and pharmacological properties. [4-6] However, synthesis of these compounds and their derivatives are now recognized as a powerful synthetic method for the heterocyclic compounds. [7-12] We have reported the synthesis of some new HHQs using K_3AlF_6 and a basic mesoporous organosilica as catalysts for the first time. [13]

K_3AlF_6 has the basicity property, so it is used in a number of organic reactions as a replacement of organic bases because of its strongly basic nature. [14-19] However, this report describes a one-pot multicomponent process for the synthesis of 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones (HHQs) derivatives using nano K_3AlF_6 as catalyst. Also, at first time, DFT calculation was carried out for the synthesized compounds. The adsorption of molecules on a surface includes complex mechanisms that comprise electrostatic interactions. Zeta potential is a measure of the magnitude of electrostatic interactions between charged surfaces that this boundary potential is known as the zeta potential. [20,21] However, in this study, to describe the mechanism, the influences of benzaldehyde, 1,3-cyclohexadione, urea with nano K_3AlF_6 on the zeta potential were also investigated.

Experimental

General

All chemical materials were purchased from Aldrich and Merck Chemical companies. Melting points were determined using an Electrothermal SI550 apparatus. FT-IR spectra were recorded from KBr discs on a Perkinelemer BX_ll. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance 500 MHz instrument in DMSO-*d6*. They are reported as follows: chemical shifts, multiplicity, coupling constants *J* (Hz), number of protons, and assignment. Mass spectra were obtained on Platform II spectrometer from Micromass; EI mode at 70 eV. UV/Vis spectra (in EtOH) were taken with a CINTRAL 101 spectrophotometer. XRD recorded by D550 Siemens and XRF spectro Xepos models. The zeta potential of biomolecules was performed using Malvern instrument in acetonitrile.

Preparation of nano K_3AlF_6

The nano K_3AlF_6 catalyst was produced according to procedure in the literature. [19,22] In this method, $KF.2H_2O$ (20 g) was dissolved in water (80 mL), and then nano basic Al_2O_3 (30 g) was added. The resulting mixture was vigorously stirred by a mechanical stirrer at 65–75 °C for 1 h. After the reaction process was completed, water was removed under reduced pressure, and the resulting powder was dried at 120 °C for 4h to produce an active K_3AlF_6 catalyst. The structure of nano K_3AlF_6 was confirmed by SEM, TEM and FT-IR spectra.

General procedure for the synthesis of some 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1H,6H)-diones (HHQs) derivatives catalyzed by nano K_3AlF_6

One pot multicomponents condensation of 1,3-cyclohexadione, benzaldehyde and urea was investigated in the presence of nano K_3AlF_6. (Table 1) The best condition was achieved using mixture of the following materials as aldehyde (10 mmol), 1,3-cyclohexadione (10 mmol), urea (12 mmol) and nano K_3AlF_6(0.025 g) in acetonitrile (10 mL) under reflux condition. The progress of the reaction was followed by TLC using *n*-hexane/ethyl acetate (5:1) as eluents until the total disappearance of the 1,3-cyclohexadione. (Scheme 1) The results are reported in Table 3. All the products are characterized by m.p, UV-vis, FT-IR and ^{1}H-NMR, ^{13}C-NMR and MS.

Table 1. nano K_3AlF_6 catalyzed synthesis of 4-phenyl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-dioneproduct (2**a**) under different conditions.

Comp.	Amount of catalyst (g)	T (˚C)	Solvent (mL)	Yield (%) [a]	Time (min) [b]
2a	0.1	r.t	Solvent free	45	135
2a	0.1	100	Solvent free	52	120
2a	0.1	Reflux	H_2O (10)	70	105
2a	0.1	Reflux	EtOH (10)	72	115
2a	0.1	Reflux	CH_3CN (10)	95	105
2a	0.05	Reflux	CH_3CN (10)	90	100
2a	0.025	Reflux	CH_3CN (10)	95	90

a. Isolated Yield; b. Times are given after maximum progress of reaction.

Proposed a mechanism of synthesis of some 4-aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1H,6H)-diones using nano K_3AlF_6.

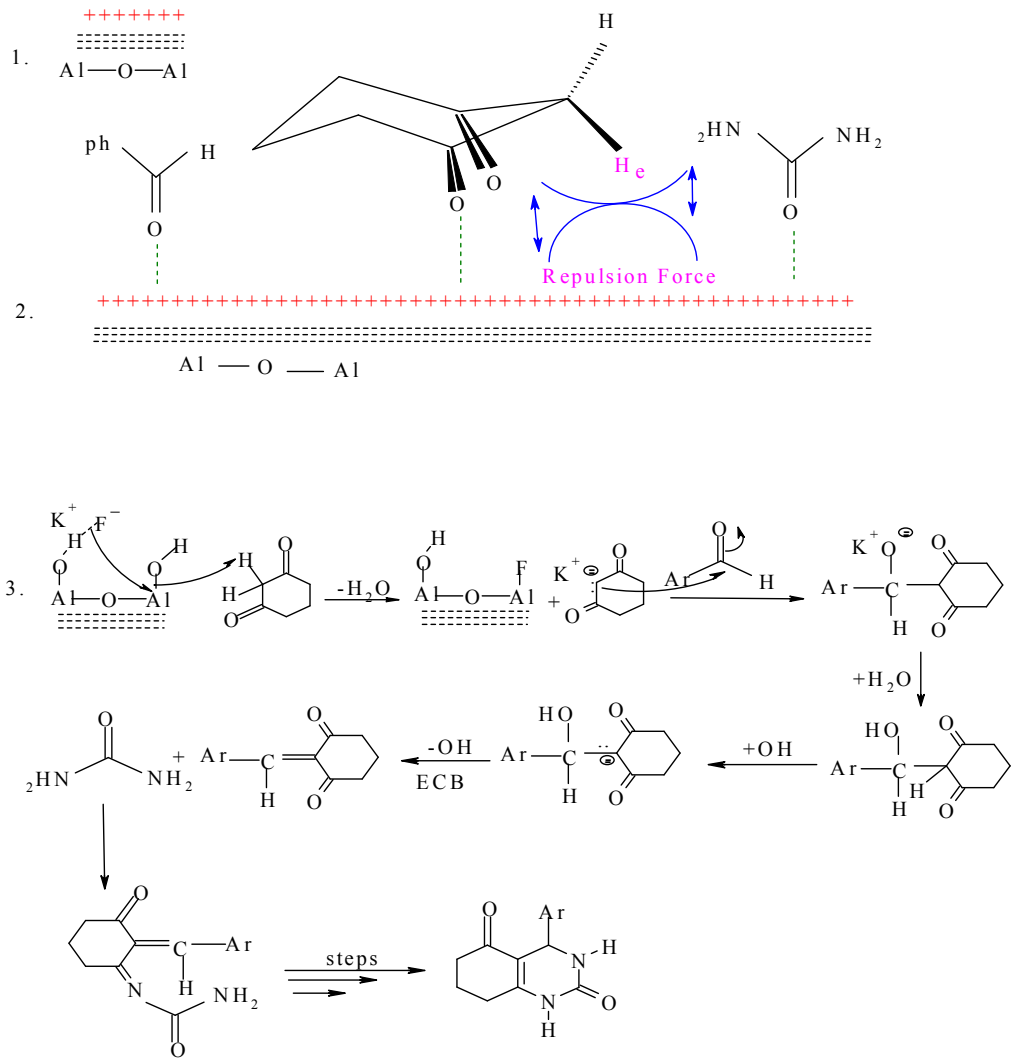
In this study for proposed mechanism of the synthesis, the zeta potentials were performed using Zetasizer Malvern Instruments. The zeta potential changes of K_3AlF_6, K_3AlF_6@benzaldehyde, K_3AlF_6@1,3-cyclohexadiones and K_3AlF_6@urea in acetonitrile are reported in Table 2.

Table 2. Zeta potential of some complex compounds in acetonitrile.

Compound	K_3AlF_6	K_3AlF_6@benzaldehyde	K_3AlF_6@1,3-cyclohexadiones	K_3AlF_6@urea
Zeta potential (mV)	+13.2	-37.2	+13.4	+40.76

Data reported in the Table 2 show that;

1. Charge density on the surface of K_3AlF_6 is positive.
2. The interaction of benzaldehyde with the catalyst is higher than that of 1,3-cyclohexadiones and urea.
3. Inter-hydrogen repulsion (H_e) with the catalyst surface appears to prevent the 1,3-cyclohexadione from interacting well with the surface.
4. One of the steps of the compression reaction is through the ECB (elimination by generation of carbanion) mechanism. (Scheme 1)



Scheme 1. Proposed mechanism of synthesis of some 4-aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones using nano K_3AlF_6.

Table 3.nano K_3AlF_6 catalyzed synthesis of some 4-aryl-3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones **2a-p.**

Comp.	Ar	Time (min)	Yield%	M.p (˚C) [a]
2a	C_6H_5-	90	95	227-229
2b	4-CH_3-C_6H_4-	50	90	190-193
2c	3-CH_3-C_6H_4-	80	85	210-212
2d	2-CH_3-C_6H_4-	50	90	218-220
2e	4-CH_3O-C_6H_4-	90	85	198-202
2f	3-CH_3O-C_6H_4-	90	85	198-202
2g	2-CH_3O-C_6H_4-	50	95	208-209
2h	4-Cl-C_6H_4-	60	95	231-234
2i	3-Cl-C_6H_4-	50	85	218-219
2j	2-Cl-C_6H_4-	55	80	221-223
2k	4-Br-C_6H_4-	85	85	215-216
2l	3-Br-C_6H_4-	50	90	214-215
2m	2-Br-C_6H_4-	65	90	218-220
2n	4-NO_2-C_6H_4-	60	85	224-226
2o	3-NO_2-C_6H_4-	65	80	215-217
2p	2,6-Cl_2-C_6H_3-	85	80	248-250

a. Ref. [13]

Table 4. Recyclability ofnano K_3AlF_6 for synthesis of some 4-aryl-3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones. (**2a).**

Entry	Amount of catalyst (g)	T (˚C)	Solvent (mL)	Yield (%) [a]	Time (min) [b]
1	0.025	Reflux	CH_3CN (10)	95	90
2	0.025	Reflux	CH_3CN (10)	90	105
3	0.025	Reflux	CH_3CN (10)	90	110
4	0.025	Reflux	CH_3CN (10)	80	125

a. Isolated Yield; b. Times are given after maximum progress of reaction.

Comparison of nano K_3AlF_6 with K_3AlF_6 in this reaction

In Table 5, reaction time and yield of products of these compounds (2**a-p**) are reported by using K_3AlF_6 [13] and nanoK_3AlF_6.

Table 5. Comparison of K_3AlF_6 (A)and nano K_3AlF_6 (B)catalyzed synthesis ofsome 4-aryl-3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones **2a-p.**

Comp.	Ar	Time		Yield %	
		A (h)	B (min)	A	B
2a	C_6H_5-	2	90	80	95
2b	4-CH_3-C_6H_4-	2.5	50	82	90
2c	3-CH_3-C_6H_4-	3	80	85	85
2d	2-CH_3-C_6H_4-	2	50	83	90
2e	4-CH_3O-C_6H_4-	3	90	85	85
2f	3-CH_3O-C_6H_4-	2.5	90	75	85
2g	2-CH_3O-C_6H_4-	2.5	50	75	85
2h	4-Cl-C_6H_4-	2	60	82	95
2i	3-Cl-C_6H_4-	2.15	50	80	85
2j	2-Cl-C_6H_4-	2	55	85	80
2k	4-Br-C_6H_4-	2	85	77	85
2l	3-Br-C_6H_4-	2.5	50	87	90
2m	2-Br-C_6H_4-	2.5	65	84	90
2n	4-NO_2-C_6H_4-	2	60	85	85
2o	3-NO_2-C_6H_4-	2.5	65	80	80
2p	2,6-Cl_2-C_6H_3-	2	85	75	80

According to reported data in Table 5, it can be suggested that the 4-aryl-3,4,6,7,8-hexahydroquinazolin-2,5-diones derivatives can be synthesized using the nano K_3AlF_6 catalyst.

Characterization of nano K_3AlF_6

The structure and morphology of nano K_3AlF_6 catalyst was studied by X-ray diffraction (XRD), X-ray fluorescence (XRF), Infrared spectroscopy (FT-IR), Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM).

i) Characterization of FT-IR spectroscopy data

These data confirm the structure of K_3AlF_6 compound.

FT-IR (KBr): 3458.59 (stretch, O-H), 604.94-639.94 (Stretch Al-O-Al).

ii) Characterization of X-ray diffraction (XRD)

X-ray diffraction (XRD) analysis showed that the catalyst has a strong peak at position of $2\theta \approx 25°$, which corresponds to K_3AlF_6 structure [23] (Figure 1).

iii) Characterization of morphology and particle size of nano K_3AlF_6 catalyst

The morphology and particle size of nano K_3AlF_6 catalyst were investigated by TEM and SEM. The average K_3AlF_6 particle sizes are changed from 17.16 to 40.40 nm (Figure 2).

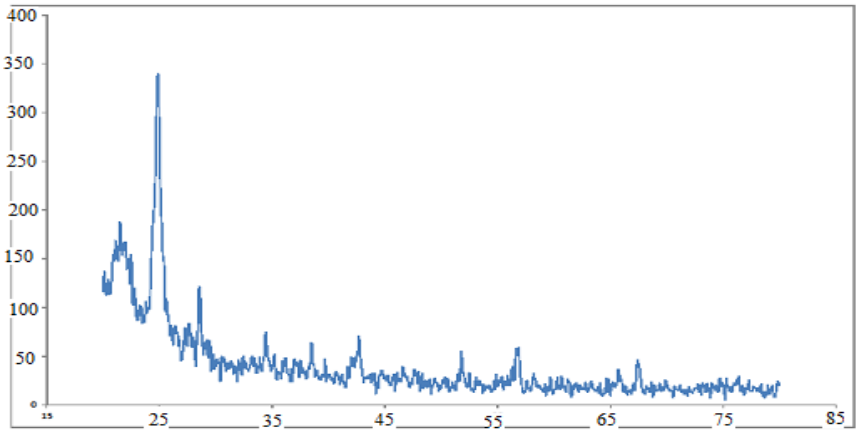
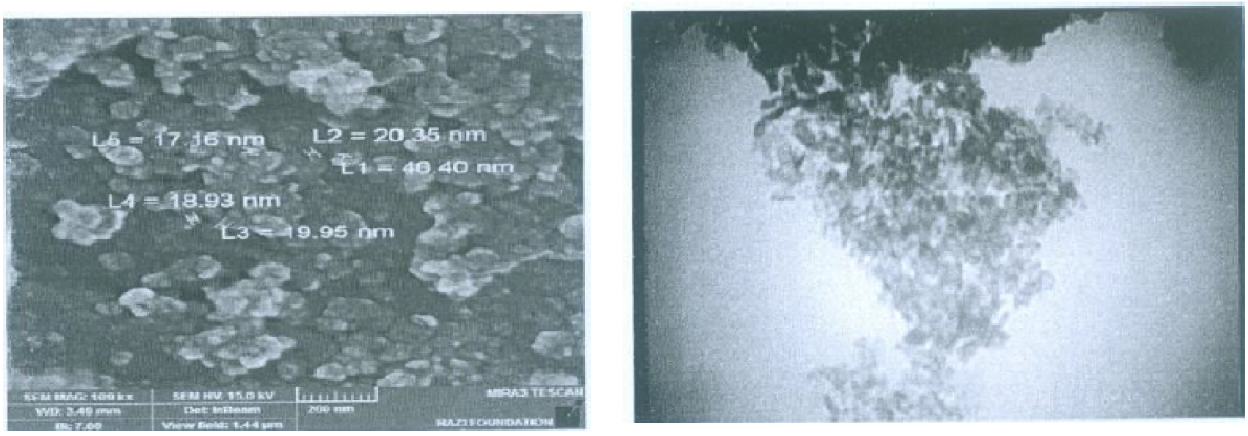


Figure 1*:* XRD pattern of nano K_3AlF_6.



a b

Figure 2. SEM (a) and TEM (b) images of nano K_3AlF_6.

Elemental analysis was carried out by X-ray fluorescence (XRF) and quantification of elements in the catalyst was determined: Al (37.19%), K(13.80%), Al_2O_3 (70.25%) and K_2O (16.63%)

Spectroscopic data

*4-phenyl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1H,6H)-diones(2**a**)*

M.P. = (227˚C - 229˚C, lit. [24] 226 – 228 ˚C). -FT-IR (KBr): 3380.25, 2920.93, 1725.05, 1710.01, 1610.17 cm^{-1}. -UV/Vis (EtOH): λ_{max} ($\log_{\varepsilon}$) = 265.66 nm (5.50).

*4-(4-methylphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1H,6H)-diones(2**b**)*

-FT-IR (KBr): 3336.85, 2941.02,1722.08, 1602.37 cm^{-1}. -^{1}H NMR (500 MHz, DMSO-d_6): δ= 1.90 (m, *J*=7Hz, 2H, H-8), 2.01 (m, 2H, H-7), 2.19 (m, 2H, H-6), 2.36 (m, 3H, CH_3), 2.94 (d, *J*=10.7 Hz, 1H, H-4), 3.90 (d , *J*=9.6 Hz, 1H, NH), 6.83 (s,1H, NH), 6.94 (m, 2H, Ar-H), 7.08 ppm (m, 2H, Ar-H). -^{13}C NMR (125 MHz, DMSO-d_6): δ= 20.20, 21.02, 29.05, 32.38, 33.50, 35.41, 37.24, 60.54, 100.45, 101.41, 116.39, 128.08, 128.35, 128.72, 134.02, 134.41, 141.68, 142.60, 195.83, 205.25 ppm. -MS (EI, 70 eV): *m/z* (%): 255.1 ($M^{+\cdot}$, $C_{15}H_{15}N_2O_2$), 253.2 ($M^{+\cdot}$ – 2H), 240.1 ($M^{+\cdot}$ – $C_{15}H_{14}NO_2$), 227.2($M^{+\cdot}$ – $C_{15}H_{15}O_2$), 164.1 ($M^{+\cdot}$ – C_7H_7),148.1 ($M^{+\cdot}$ – C_7H_7-CH-NH-CO-NH), 131.1 ($M^{+\cdot}$ – C_7H_7-CH-CH=CH_2), 119.1 ($M^{+\cdot}$ – C_7H_7-CH-NH), 71.1 ($M^{+\cdot}$ – NH-CH=CH-COH), 70.1 ($M^{+\cdot}$ – CH_3-CO-CH=CH_2), 57.1 ($M^{+\cdot}$ – NH-CO-NH), 51.1 ($M^{+\cdot}$ – CH_2=CH-COH), 42.1 ($M^{+\cdot}$ – CH_2-CH_2-CH_2). -UV/Vis (EtOH): λ_{max} ($\log_\varepsilon$) = 257.98 nm (5.49).

*4-(3-methylphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1H,6H)-diones (2**c**)*

-FT-IR (KBr): 3359.99, 2975.01, 1720.79, 1609.14 cm^{-1}.-^{1}H NMR(500MHz, DMSO-d_6): δ=1.89 (m, 2H, H-8), 2.10 (m, 2H, H-7), 2.16 (m, 2H, H-6), 2.38 (m, 3H, CH_3), 2.99 (d, *J*=10.65 Hz, 1H, H-4), 3.90 (d, *J*=9.6 Hz, 1H, NH), 6.78 (s, 1H, NH), 6.84 (m, 1H , Ar-H), 6.91 (m, 1H, Ar-H), 7.00 (m, 1H, Ar-H), 7.04 (m, 1H, Ar-H).-^{13}C NMR (125 MHz, DMSO-d_6): δ=20.40, 21.63, 28.95, 29.09, 32.68, 33.44, 35.39, 37.24, 100.44, 101.39, 111.57, 116.38, 125.43, 126.02, 127.58, 128.79, 129.43, 136.45, 144.74, 145.63, 167.72, 169.47, 189.82, 195.86, 196.27, 205.22, 206.67 ppm. -MS (EI, 70 eV): *m/z* (%): 255.2 ($M^{+\cdot}$; $C_{15}H_{15}N_2O_2$), 253.2 ($M^{+\cdot}$ – 2H), 240.1 ($M^{+\cdot}$ – $C_{15}H_{14}NO_2$), 227.2 ($M^{+\cdot}$ – $C_{15}H_{15}O_2$), 164.1 ($M^{+\cdot}$ –C_7H_7), 148.1 ($M^{+\cdot}$ – C_7H_7-CH-NH-CO-NH), 131.1 ($M^{+\cdot}$ – C_7H_7-CH-CH=CH_2), 119.1 ($M^{+\cdot}$ – C_7H_7-CH-NH), 71.1 ($M^{+\cdot}$ – NH-CH=CH-COH), 70.1 ($M^{+\cdot}$ – CH_3-CO-CH=CH_2), 57.1 ($M^{+\cdot}$ – NH-CO- NH), 51.1 ($M^{+\cdot}$ – CH_2=CH-COH), 42.1 ($M^{+\cdot}$ – CH_2-CH_2-CH_2). -UV/Vis (EtOH): λ_{max} ($\log_\varepsilon$)=268.22 nm (5.50).

*4-(2-methylphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1H,6H)-diones (2**d**)*

-FT-IR (KBr): 3314.86, 2936.99, 1712.01, 1617.22 cm^{-1}.-^{1}H NMR(500 MHz, DMSO-d_6): δ=1.84(m, 2H, H-8), 2.08 (m, 2H, H-7), 2.20 (m, 2H, H-6), 2.36 (m, 3H, CH_3), 3.15 (d, *J*=10.9 Hz, 1H, H-4), 4.01 (d, *J*=10.65 Hz, 1H, NH), 6.90 (s, 1H, NH), 6.93 (m, 1H, Ar-H), 6.97 (m, 1H, Ar-H), 7.02 (m, 2H, Ar-H). -^{13}C NMR (125 MHz, DMSO-d_6): δ=20.69, 21.35, 28.95, 29.48, 35.98, 37.82, 61.81, 101.07, 101.89, 112.77, 118.22, 125.72, 126.18, 130.13, 135,49, 139.36, 144.54, 167.67, 169.97, 196.42, 206.32 ppm. -MS (EI, 70 eV): *m/z* (%): 255.1 ($M^{+\cdot}$; $C_{15}H_{15}N_2O_2$), 253.2 ($M^{+\cdot}$ - 2H), 240.1 ($M^{+\cdot}$ – $C_{15}H_{14}NO_2$), 227.2 ($M^{+\cdot}$ – $C_{15}H_{15}O_2$), 164.1 ($M^{+\cdot}$ – C_7H_7), 148.1($M^{+\cdot}$ – C_7H_7-CH-NH-CO-NH), 131.1 ($M^{+\cdot}$ – C_7H_7-CH-CH=CH_2), 119.1 ($M^{+\cdot}$ – C_7H_7-CH-NH), 71.1 ($M^{+\cdot}$ – NH-CH=CH-

COH), 70.1 ($M^{+\cdot}$ – CH_3-CO-CH=CH_2), 57.1 ($M^{+\cdot}$ – NH-CO-NH), 51.1 ($M^{+\cdot}$ – CH_2=CH-COH), 42.1 ($M^{+\cdot}$ – CH_2-CH_2-CH_2). -UV/Vis (EtOH): λ_{max} ($\log_\varepsilon$)=258.40 nm (5.49).

*4-(4-methoxyphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1H,6H)-diones (2**e**)*

-FT-IR (KBr): 3389.23, 2959.93, 1722.04, 1601.58, 1375.17 cm^{-1}.-^{1}H NMR (500 MHz, DMSO-d_6): δ=1.86 (m, 2H, H-8), 2.15 (m, H-7), 2.39 (m, 2H, H-6), 2.96 (d, *J*=10.7 Hz, 1H, H-4), 3.68 (s, 3H, OCH_3), 3.88 (d, *J*=10.75 Hz, 1H, NH), 6.75 (m, 2H, Ar-H), 6.84 (s, 1H, NH), 7.10 (m, 2H, Ar-H). -^{13}C NMR (125 MHz, DMSO-d_6): δ=20.99, 29.07, 31.97, 32.18, 35.41, 37.16, 55.38, 60.58, 100.50, 101.44, 113.71, 116.25, 129.70, 137.51, 157.37, 167.61, 195.87, 205.37 ppm. -MS (EI, 70 eV): *m/z* (%): 271.1 (M^+, $C_{15}H_{15}N_2O_3$), 269.2 (M^+ –2H), 256.1($M^{+\cdot}$ – $C_{15}H_{14}NO_3$), 255.1 ($M^{+\cdot}$ – CH_3), 243.1 ($M^{+\cdot}$ – $C_{15}H_{15}O_3$), 164.1 ($M^{+\cdot}$ – C_7H_7O-CH-NH-CO-NH), 147.1 ($M^{+\cdot}$ – C_7H_7O-CH-CH=CH_2), 135.1 ($M^{+\cdot}$ – C_7H_7O-CH-NH), 107.1 ($M^{+\cdot}$ – C_7H_7O), 71.1 ($M^{+\cdot}$ – NH-CH=CH-COH), 70.1 ($M^{+\cdot}$ – CH_3-CO-CH=CH_2), 57.1 ($M^{+\cdot}$ – NH-CO-NH), 51.1 ($M^{+\cdot}$ – CH_2=CH-COH), 42.1 ($M^{+\cdot}$ – CH_2-CH_2-CH_2). -UV/Vis (EtOH): λ_{max} ($\log_\varepsilon$)=265.66 nm (5.50).

*4-(3-methoxyphenyl)-1,3,4,6,7,8-hexahydroquinazolin-2,5(1H,6H)-diones (2**f**)*

-FT-IR (KBr): 3374.80, 2941.18, 1719.71, 1614.34, 1374.19 cm^{-1}. -^{1}H NMR (500 MHz, DMSO-d_6): δ=1.89 (m, 2H, H-8), 2.16 (m, 2H, H-7) 2.39 (m, 2H, H-6), 2.98 (d, *J*=10.7 Hz, 1H, H-4), 3.69 (s, 3H, OCH_3), 3.91 (d, *J*=10.6 Hz, 1H, NH), 6.85 (s, 1H, NH), 6.62 (m, 1H, Ar-H), 6.73 (s, 1H, Ar-H),6.79 (d, *J*=6.55 Hz, 1H, Ar-H),7.07 (t, *J*=6.85 Hz, 1H, Ar-H). -^{13}CNMR (125 MHz, DMSO-d_6): δ=20.27, 21.09, 28.98, 29.12, 32.67, 33.47, 35.42, 36.15, 37.27, 55.22, 59.66, 60.38, 100.48, 101.24, 110.36, 111.54, 114.47, 115.04, 116.00, 120.72, 121.33, 128.64, 146.48, 147.31, 159.11, 167.90, 169.59, 189.83, 195.92, 196.31, 205.29, 206.66 ppm. -MS (EI, 70 eV): *m/z* (%): 271.1(M^+, $C_{15}H_{15}N_2O_3$), 269.2 (M^+ –2H), 256.1 ($M^{+\cdot}$ – $C_{15}H_{14}NO_3$), 255.1 ($M^{+\cdot}$ – CH_3), 243.2 ($M^{+\cdot}$ – $C_{15}H_{15}O_3$), 164.1 ($M^{+\cdot}$ – C_7H_7O-CH-NH-CO-NH), 147.1 ($M^{+\cdot}$ – C_7H_7O-CH-CH=CH_2), 135.1 ($M^{+\cdot}$ – C_7H_7O-CH-NH), 107.1 ($M^{+\cdot}$ – C_7H_7O), 71.1 ($M^{+\cdot}$ – NH-CH=CH-COH), 70.1 ($M^{+\cdot}$ – CH_3-CO-CH=CH_2), 57.1 ($M^{+\cdot}$ – NH-CO-NH), 51.1 ($M^{+\cdot}$ – CH_2=CH-COH), 42.1 ($M^{+\cdot}$ – CH_2-CH_2-CH_2). -UV/Vis (EtOH): λ_{max} ($\log_\varepsilon$)=275.12 nm(5.49).[12-13]

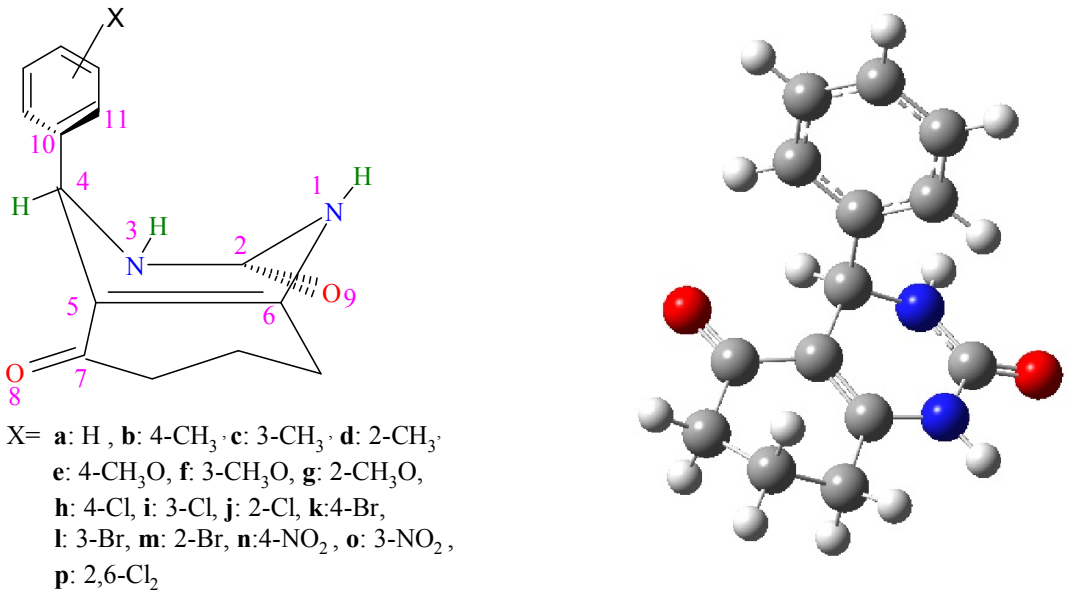
Theoretical section

Cytosine natural products comprise an intriguing class of structurally diverse marine alkaloids possessing varied and potent biological activities. Also, this compound found in the DNA and RNA. Polycyclic hexahydroquinazolin-2,5(1*H*,6*H*)-diones form a class of intriguing heterocylic compounds that have attracted considerable attention in recent years. Because these compounds

have the cytosine core, 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones derivatives (HHQs)have occupied an important position in natural and synthetic organic chemistry.

The structure of HHQs are similar to 3,4-dihydropyrimidinones compounds. Configuration of the C4 position in the heterocyclic core of DHPMs can be affected in the biological activities of these compounds. Furthermore, structural studies of several DHPMs have shown that the configuration of the substituent at C4 position plays a major role in their pharmacological activity. Experimental data of individual pure enantiomers, referenced to samples of known absolute configuration, have proven useful for determination of the absolute configuration in various biologically active DHPM derivatives. These data show that, only molecules with R configuration act as calcium channel modulators. [25-29] Also, the results of computational theory methods carried out on the conformational analysis of some DHPMs are in agreement with experimental data. [3, 30, 31] Due to the importance of the configuration of the aryl group at the C4 position and substituent at C5 of the heterocyclic ring for the biological and pharmacological activities of DHPMs, in the present work we have used B3LYP/6-31G(d,p) computations to study structure bonding, as well as spectroscopic characteristics of a series of some new 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones derivatives (HHQs) [31]

General structures of the new HHQs with aryl-up (antagonist) conformation studied are shown in Figure 3. To identify the structure of these compounds, it is necessary to study the characteristics of bond lengths, angles, and some electronic parameters.



X= **a**: H , **b**: 4-CH_3, **c**: 3-CH_3, **d**: 2-CH_3,
e: 4-CH_3O, **f**: 3-CH_3O, **g**: 2-CH_3O,
h: 4-Cl, **i**: 3-Cl, **j**: 2-Cl, **k**:4-Br,
l: 3-Br, **m**: 2-Br, **n**:4-NO_2, **o**: 3-NO_2,
p: 2,6-Cl_2

Figure 3. General structure of 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones derivatives.

Results and discussion

The general structure of HHQs, which the numbering scheme was introduced to describe these structures, is shows in the Figure 3. Analysis of the optimized structures of HHQs show that

a) The heterocylic ring adopts a boat conformation,
b) Flattened at N1 toward an envelope conformation,
c) With a pseudo-axial orientation of the C4 substituent, (Table 6 calculated of Δ)
d) In all derivatives the C4 substituent adopts an up orientation with respect to the heterocyclic ring boat plane.

However, the same structural trends had already been observed for the 3,4-dihydropyrimidinones (DHPMs). This orientation corresponds to the antagonist activity of the same DHPMs compounds. [32,33]

The lengths of the C7=O8, C5=C6, C2=O9, N1–H, N3–H, and C4–H bonds that play a role in the activities of HHQs are optimized. (Table 5) The optimum values of dihedral angles C6–C5–C7–O8, C11–C10–C4–N3, and C11–C10–C4–C5 which denoted as α, β, and γ, respectively were also reported in Table 5. These data reflected the orientations of the carbonyl group and the aryl ring on the C5 and C4 positions with respect to the heterocyclic ring. The optimum values of the dihedral angle β show that the aryl and heterocyclic ring are not perpendicular to each other. Furthermore, the deviation of an aryl ring from 90 ˚ (denoted by Δ) towards the N3 and C5 atom was calculated:

$$\Delta = \gamma + \beta$$

Table 6. Selected B3LYP/6-31G(d,p) optimized geometrical parameters obtained for HHQs (bond lengths and angles are given in Å and degrees, respectively).

Comp.	X	N1-H	N3-H	C4-H	C2=O9	C7=O8	(-) α	(-) β	γ	Δ
2a	H	1.0096	1.0100	1.0953	1.2485	1.2565	174.20	31.76	91.61	59.86
2b	4-CH_3	1.0095	1.0100	1.0954	1.2487	1.2565	174.16	32.48	90.91	58.43
2c	3-CH_3	1.0095	1.0100	1.0954	1.2486	1.2564	174.15	33.31	90.13	56.82
2d	2-CH_3	1.0094	1.0100	1.0923	1.2486	1.2563	174.39	60.15	62.93	2.78
2e	4-CH_3O	1.0095	1.0100	1.0955	1.2486	1.2565	174.56	30.59	92.77	62.18
2f	3-CH_3O	1.0095	1.0099	1.0950	1.2486	1.2560	174.08	30.33	92.85	62.52
2g	2-CH_3O	1.0096	1.0110	1.0947	1.2492	1.2547	176.48	116.74	7.30	114.04
2h	4-Cl	1.0096	1.0110	1.0953	1.2475	1.2555	174.80	27.80	92.90	65.10
2i	3-Cl	1.0097	1.0100	1.0952	1.2478	1.2566	174.89	27.54	95.66	68.12
2j	2-Cl	1.0097	1.0105	1.0937	1.2475	1.2540	177.62	103.85	19.98	-83.87
2k	4-Br	1.0097	1.0100	1.0953	1.2478	1.2569	175.02	28.49	94.80	66.31
2l	3-Br	1.0097	1.0100	1.0952	1.2478	1.2565	174.78	28.02	95.20	67.18
2m	2-Br	1.0097	1.0109	1.0944	1.2475	1.2542	177.15	106.83	17.19	-89.64
2n	4-NO_2	1.0100	1.010	1.0954	1.2468	1.2567	175.09	28.29	95.01	66.72
2o	3-NO_2	1.0098	1.0101	1.0952	1.2472	1.2560	175.41	32.00	91.29	59.29

Vibration analysis was carried out on the optimized geometries of the HHQs at B3LYP/6-31G(d,p) level of theory. The calculated harmonic frequencies for HHQs were reported in Table 6. As expected, the calculated vibrational frequencies show the dependence on the type and position of the substituent. In all HHQs the frequency of:

1) The N1–H bond stretching mode is rather larger than that of the N3–H bond. This can be attributed to the tighter conjugation of the N1 atom with the C5=C6 bond and the C7=O8 group, as compared with that of the N3 atom, which results in a stronger N1–H bond.
2) The conjugated of C=C and lone pair electron on the N atom can be effected on the frequencies of C=O. Analysis of data shows that the smaller frequencies of the stretching mode of the C7=O8 group, as compared with those of the C2=O9 group, can also be attributed to the fact that the C7=O8 bond is conjugated with the C5=C6 group and N1 atom, while the C2=O9 bond is conjugated only to the N3 atom.

Table 7. Calculated harmonic frequencies (cm^{-1}) obtained for the B3LYP/6-31G(d,p) optimized structures of HHQs.

Comp.	X	N1-H	N3-H	C4-H	C2=O9	C7=O8	C5=C6
2a	H	3645.91	3641.91	3075.00	1756.8	1650.3	1694.4
2b	4-CH_3	3646.0	3642.0	3074.6	1756.5	1650.0	1694.4
2c	3-CH_3	3646.5	3642.1	3074.4	1757.0	1650.6	1697.3
2d	2-CH_3	3647.8	3641.5	3111.2	1757.5	1651.7	1696.8
2e	4-CH_3O	3646.2	3641.9	3074.1	1755.9	1650.2	1697.4
2f	3-CH_3O	3645.4	3639.6	3087.9	1756.5	1660.6	1695.5
2g	2-CH_3O	3645.6	3642.8	3081.0	1756.1	1651.2	1699.0
2h	4-Cl	3644.2	3643.0	3077.5	1756.2	1646.3	16951.8
2i	3-Cl	3644.0	3641.9	3078.8	1757.3	1649.4	1698.2
2j	2-Cl	3643.6	3637.3	3099.6	1757.6	1661.1	1968.1
2k	4-Br	3644.3	3641.8	3077.3	1757.4	1649.1	1697.4
2l	3-Br	3644.1	3641.9	3078.8	1757.3	1650.0	1697.7
2m	2-Br	3643.8	3625.6	3089.3	1758.2	1661.1	1698.2
2n	4-NO_2	3642.5	3640.8	3077.0	1759.1	1646.9	1696.2
2o	3-NO_2	3643.8	3641.0	3078.0	1758.1	1651.6	1699.4
2p	2,4-Cl_2	3643.5	3641.5	3079.4	1758.9	1652.5	1698.5

Second order perturbation theory analysis of Fock matrix with NBO basis

The second order Fock matrix was carried out to evaluate the donor–acceptor interactions in the NBO analysis. The interaction result is a loss of occupancy from the localized NBO of the idealized Lewis structure into an empty non- Lewis orbital. For each donor (i), and acceptor (j), the stabilization energy E(2) associated with the delocalization i-j is estimated as:

$E^2 = \Delta E_{ij} = q_i F(i,j)^2/\varepsilon_j - \varepsilon_i$

Natural bond orbital analysis provides an efficient method for

i) studying intra and intermolecular bonding

ii) interaction among bonds

iii) provides a convenient basis for investigating charge transfer or conjugative interaction in molecular systems.

iv) delocalization of electron density between occupied Lewis-type (bond or lone pair) NBO orbitals and formally unoccupied (anti-bond or Rydgberg) non-Lewis NBO orbitals correspond to a stabilizing donor–acceptor interaction. [34-37]

Some electron donor orbital, acceptor orbital and the interacting stabilization energy resulted from the second order micro disturbance theory are where q_i is the donor orbital occupancy, are ε_i and ε_j diagonal elements and F(i,j) is the off diagonal NBO Fock matrix element reported. [36-38] The larger the E(2) value, the more intensive is the interaction between electron donors and electron acceptors, that shows

A) more donating tendency from electron donors to electron acceptors

B) the greater the extent of conjugation of the whole system.

NBO analysis has been performed on the 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5(1*H*,6*H*)-diones derivative (HHQs) molecules at the DFT/B3LYP/6-31G(d,p) level in order to elucidate the delocalization of electron density within the molecules. (Tables 8).

Table 8. Second order perturbation theory analysis of Fock matrix with NBO basis.

Comp.	X	Donor (i)	Acceptor (j)	E2 Kcal/mol	E (j)-(i) a.u	F (i.j) a.u
2a	H	σ (C4-N3)	π* (C2=O9)	3.81	1.97	0.077
		σ (C6-N1)	π* (C2=O9)	2.14	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N3-H)	(C2)	1.05	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.26	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.74	1.54	0.121
2b	4-CH_3	σ (C4-N3)	π* (C2=O9)	3.62	1.97	0.077
		σ (C6-N1)	π* (C2=O9)	2.13	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N3-H)	(C2)	1.05	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.26	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.73	1.54	0.120
2c	3-CH_3	σ (C4-N3)	π* (C2=O9)	3.81	1.98	0.077
		σ (C6-N1)	π* (C2=O9)	2.13	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N3-H)	(C2)	1.05	1.29	0.033
		σ (N1-H)	π* (C5=C6)	0.51	1.17	0.022
		π (C5=C6)	π* (C7=O8)	28.73	1.54	0.121
2d	2-CH_3	σ (C4-N3)	π* (C2=O9)	3.81	1.98	0.077

		σ (C6-N1)	π* (C2=O9)	2.13	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N3-H)	(C2)	1.05	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.27	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.83	1.54	0.121
2e	4-CH_3O	σ (C4-N3)	π* (C2=O9)	3.84	1.97	0.077
		σ (C6-N1)	π* (C2=O9)	2.14	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.16	0.022
		σ (N3-H)	(C2)	1.06	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.25	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.73	1.54	0.121
2f	3-CH_3O	σ (C4-N3)	π* (C2=O9)	3.85	1.98	0.078
		σ (C6-N1)	π* (C2=O9)	2.14	1.32	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.16	0.022
		σ (N3-H)	(C2)	1.06	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.25	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.65	1.54	0.119
2g	2-CH_3O	σ (C4-N3)	π* (C2=O9)	4.18	1.95	0.082
		σ (C6-N1)	π* (C2=O9)	2.00	1.32	0.046
		σ (N1-H)	(C2)	0.85	1.32	0.030
		σ (N3-H)	(C2)	1.09	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.31	1.29	0.059
		π (C5=C6)	π* (C7=O8)	28.31	1.55	0.119
2h	4-Cl	σ (C4-N3)	π* (C2=O9)	3.63	1.98	0.076
		σ (C6-N1)	π* (C2=O9)	2.25	1.33	0.049
		σ (N1-H)	π* (C2=O9)	0.76	0.71	0.022
		σ (N3-H)	(C2)	0.81	1.29	0.029
		σ (N1-H)	π* (C5=C6)	3.05	1.31	0.056
		π (C5=C6)	π* (C7=O8)	24.16	1.33	0.113
2i	3-Cl	σ (C4-N3)	π* (C2=O9)	3.76	1.99	0.077
		σ (C6-N1)	π* (C2=O9)	2.16	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N3-H)	(C2)	1.05	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.26	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.80	1.54	0.120
2j	2-Cl	σ (C4-N3)	π* (C2=O9)	3.76	1.79	0.077
		σ (C6-N1)	π* (C2=O9)	2.16	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N3-H)	(C2)	1.05	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.26	1.29	0.058
		π (C5=C6)	π* (C7=O8)	1.67	1.26	0.041
2k	4-Br	σ (C4-N3)	π* (C2=O9)	3.77	1.99	0.077
		σ (C6-N1)	π* (C2=O9)	2.15	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022

		σ (N3-H)	(C2)	1.05	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.27	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.97	1.54	0.120
2l	3-Br	σ (C4-N3)	π* (C2=O9)	3.77	1.99	0.077
		σ (C6-N1)	π* (C2=O9)	2.16	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N3-H)	(C2)	0.89	1.32	0.031
		σ (N1-H)	π* (C5=C6)	3.26	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.81	1.54	0.120
2m	2-Br	σ (C4-N3)	π* (C2=O9)	3.94	1.96	0.079
		σ (C6-N1)	π* (C2=O9)	2.03	1.33	0.047
		σ (N1-H)	(C2)	0.87	1.32	0.030
		σ (N3-H)	(C2)	1.11	1.29	0.034
		σ (N1-H)	π* (C5=C6)	3.33	1.29	0.059
		π (C5=C6)	π* (C7=O8)	27.94	1.56	0.118
2n	4-NO_2	σ (C4-N3)	π* (C2=O9)	3.68	2.00	0.076
		σ (C6-N1)	π* (C2=O9)	2.16	1.33	0.048
		σ (N1-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N3-H)	(C2)	1.05	1.29	0.033
		σ (N1-H)	π* (C5=C6)	3.30	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.93	1.54	0.120
2o	3-NO_2	σ (C4-N3)	π* (C2=O9)	3.15	1.24	0.056
		σ (C6-N1)	π* (C2=O9)	2.17	1.33	0.048
		σ (N1-H)	(C2)	1.04	1.29	0.033
		σ (N3-H)	π* (C2=O9)	0.51	1.17	0.022
		σ (N1-H)	π* (C5=C6)	3.28	1.29	0.058
		π (C5=C6)	π* (C7=O8)	28.40	1.55	0.119
2p	2,4-Cl_2	σ (C4-N3)	π* (C2=O9)	3.60	1.30	0.066
		σ (C6-N1)	π* (C2=O9)	2.25	1.28	0.052
		σ (N1-H)	(C2)	1.00	1.34	0.035
		σ (N3-H)	π* (C2=O9)	0.55	1.20	0.024
		σ (N1-H)	π* (C5=C6)	3.23	1.30	0.055
		π (C5=C6)	π* (C7=O8)	28.60	1.57	0.115

The comparison of the reported data in Table 8 shows that N3-H group is a relatively more resonance with the C2=O9 group in comparison with N1-H. Also, the analysis of the data reported in this table shows that N1-H group is more tendentious to resonance with the C5=C6 group.

Furthermore, the comparison of bond lengths, vibration data and Second order perturbation theory analysis of C2=O9 and C7=O8 functional groups (Tables 6-8) show that the resonance rate is higher in the C7=O8 group.

Calculations of some parameters in solvent media

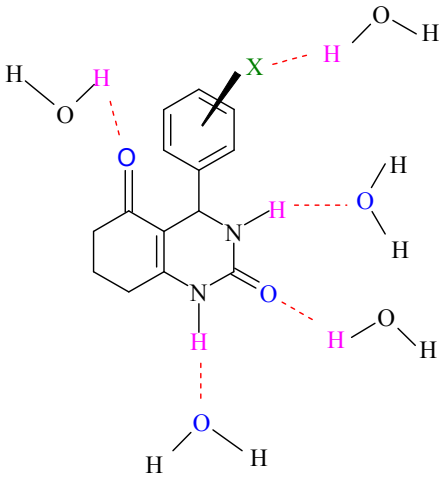
Many important chemical reactions occur in the liquid phase, and the development of accurate methods to predict the energetics of solution phase reactions is an area of active research. So, in the present work, the DFT method was used to investigate solvent effects in ethanol and water as solvent.

Table 9. Energy parameters (a.u) in solvent media.

	Vacuum			Ethanol			Water		
Comp.	HOMO	LUMO	Gap [1]	HOMO	LUMO	Gap	HOMO	LUMO	Gap
2a	-0.2330	-0.0563	0.1767	-0.2317	-0.0553	0.1764	-0.2320	-0.0552	0.1768
2b	-0.2286	-0.0550	0.1736	-0.2309	-0.0554	0.1755	-0.2311	-0.0555	0.1756
2c	-0.2305	-0.0553	0.1752	-0.2308	-0.0556	0.1752	-0.2310	-0.0557	0.1753
2d	-0.2314	-0.0558	0.1756	-0.2314	-0.0554	0.1760	-0.2313	-0.0555	0.1758
2e	-0.2144	-0.0550	0.1594	-0.2212	-0.0552	0.1660	-0.2218	-0.0554	0.1664
2f	-0.2166	-0.0543	0.1623	-0.2239	-0.0559	0.1680	-0.2241	-0.0561	0.168
2g	-0.2199	-0.0460	0.1739	-0.2275	-0.0543	0.1732	-0.2279	-0.0546	0.1733
2h	-0.2409	-0.0562	0.1847	-0.2344	-0.0584	0.1760	-0.2340	-0.0573	0.1767
2i	-0.2404	-0.0627	0.1777	-0.2349	-0.0588	0.1761	-0.2346	-0.0586	0.176
2j	-0.2384	-0.0576	0.1808	-0.2371	-0.0578	0.1793	-0.2370	-0.0578	0.1792
2k	-0.2371	-0.0624	0.1747	-0.2339	-0.0576	0.1763	-0.2337	-0.0575	0.1762
2l	-0.2391	-0.0617	0.1774	-0.2343	-0.0584	0.1759	-0.2341	-0.0582	0.1759
2m	-0.2318	-0.0539	0.1779	-0.2353	-0.0574	0.1779	-0.2352	-0.0574	0.1778
2n	-0.2498	-0.0104	0.2394	-0.2378	-0.1138	0.124	-0.2372	-0.1143	0.1229
2o	-0.2459	-0.1040	0.1419	-0.2362	-0.1137	0.1225	-0.2358	-0.1143	0.1215
2p	-0.2485	-0.0626	0.1859	-0.2390	-0.0595	0.1795	-0.2387	-0.0594	0.1793

1. $Gap=E_{LUMO}-E_{HOMO}$

The observed changes in the energy band gap (E_{LUMO}-E_{HOMO}) (Table 9) indicate that there must be an interaction between the functional groups and X substituent on the aryl ring at position 4 with the solvent. (Comparative of 2a, 2b, 2e,…) (Scheme 2).



Scheme2. Solvation of HHQs in H_2O as solvent.

Table 10. Solvation Gibbs energies ($kJ \cdot mol^{-1}$) for some HHQs compounds in solvent media.

		Solvent Free	ethanol	water	Ethanol and water
Comp.	X	G (Hartree)	G (Hartree)	G (Hartree)	$\Delta G_{solvation}$ (kJ/mol)
2a	H	-801.47	-801.46	-801.46	-26.26
2b	4-CH_3	-840.75	-840.77	-840.77	-52.51
2c	3-CH_3	-840.75	-840.77	-840.77	-52.51
2d	2-CH_3	-840.74	-840.76	-840.76	-52.51
2e	4-CH_3O	-915.92	-915.94	-915.94	-52.51
2f	3-CH_3O	-915.92	-915.94	-915.94	-52.51
2g	2-CH_3O	-915.92	-915.94	-915.94	-52.51
2h	4-Cl	-1261.02	-1261.07	-1261.07	-26.255
2i	3-Cl	-1261.05	-1261.07	-1261.07	-52.51
2j	2-Cl	-1261.05	-1261.07	-1261.07	-52.51
2k	4-Br	-3372.45	-3372.47	-3372.47	-52.51
2l	3-Br	-3372.45	-3372.47	-3372.47	-52.51
2m	2-Br	-3372.45	-3372.47	-3372.47	-52.51
2n	4-NO_2	-1005.89	-1005.91	-1005.91	-52.51
2o	3-NO_2	-1005.89	-1005.91	-1005.91	-52.51
2p	2,4-Cl_2	-1720.85	-1720.66	-1720.66	-26.26

The results reported in Table 10 and Scheme 2 indicated the effects of the functional groups and substituents on the aromatic ring with the solvent.

Table 11. Scaled frequencies calculated at the B3LYP/6-31G(d,p) level in solvent media.

Comp.	group	vacuum	ethanol	water
2a	N1-H	3645.91	3637.49	3637.18
	N3-H	3641.91	3624.34	3633.64
	C4-H	3075.00	3071.10	3070.26
	C2=O9	1756.8	1737.49	1736.56
	C7=O8	1650.3	1628.28	1626.74
	C5=C6	1694.4	1693.13	1692.63
2b	N1-H	3646.0	3636.7	3636.0
	N3-H	3642.0	3633.7	3633.3
	C4-H	3074.6	3070.3	3070.0
	C2=O9	1756.5	1721.6	1719.9
	C7=O8	1650.0	1626.7	1625.0
	C5=C6	1694.4	1684.7	1683.5
2c	N1-H	3646.5	3637.7	3636.6
	N3-H	3642.1	3634.1	3634.4
	C4-H	3074.4	3072.1	3070.5
	C2=O9	1757.0	1722.6	1720.8
	C7=O8	1650.6	1626.8	1625.3
	C5=C6	1697.3	1648.9	1683.7
2d	N1-H	3647.8	3637.9	3637.5
	N3-H	3641.5	3632.1	3631.8
	C4-H	3111.2	3044.0	3043.6
	C2=O9	1757.5	1726.4	1721.9
	C7=O8	1651.7	1626.7	1624.9
	C5=C6	1696.8	1682.5	1681.3
2e	N1-H	3646.2	3639.0	3638.0
	N3-H	3641.9	3633.9	3633.5
	C4-H	3074.1	3071.5	3069.8
	C2=O9	1755.9	1722.1	1720.6
	C7=O8	1650.2	1626.6	1625.1
	C5=C6	1697.4	1684.2	1633.1
2f	N1-H	3645.4	3636.4	3635.4
	N3-H	3639.6	3632.3	3632.1
	C4-H	3087.9	3074.7	3074.5
	C2=O9	1756.5	1722.6	1721.0
	C7=O8	1660.6	1627.7	1625.7
	C5=C6	1695.5	1685.2	1684.0
2g	N1-H	3645.6	3637.0	3636.3
	N3-H	3642.8	3624.5	3624.0
	C4-H	3081.0	3085.9	3085.2

	C2=O9	1756.1	1720.9	1719.6
	C7=O8	1651.2	1626.4	1624.4
	C5=C6	1699.0	1683.8	1682.8
2h	N1-H	3644.2	3636.6	3637.2
	N3-H	3643.0	3634.2	3633.8
	C4-H	3077.5	3076.8	3075.4
	C2=O9	1756.2	1724.6	1723.8
	C7=O8	1646.3	1624.1	1623.2
	C5=C6	1695.2	1683.4	1683.5
2i	N1-H	3644.0	3634.5	3635.7
	N3-H	3641.9	3636.8	3633.5
	C4-H	3078.8	3075.6	3074.9
	C2=O9	1757.3	1724.8	1723.1
	C7=O8	1649.4	1624.7	1623.8
	C5=C6	1698.2	1684.5	1684.0
2j	N1-H	3643.6	3631.4	3633.2
	N3-H	3637.3	3633.5	3631.0
	C4-H	3099.6	3101.2	3101.0
	C2=O9	1757.6	1723.3	1721.9
	C7=O8	1661.1	1630.0	1628.1
	C5=C6	1968.1	1684.9	1684.1
2k	N1-H	3644.3	3637.9	3637.1
	N3-H	3641.8	3634.7	3634.6
	C4-H	3077.3	3072.0	3071.5
	C2=O9	1757.4	1723.7	1721.9
	C7=O8	1649.1	1684.6	1625.1
	C5=C6	1697.4	1626.9	1683.4
2l	N1-H	3644.1	3635.8	3636.7
	N3-H	3641.9	3633.7	3634.3
	C4-H	3078.8	3075.3	3074.4
	C2=O9	1757.3	1724.5	1723.1
	C7=O8	1650.0	1625.3	1623.8
	C5=C6	1697.7	1683.8	1683.2
2m	N1-H	3643.8	3635.8	3635.3
	N3-H	3625.6	3618.4	3618.2
	C4-H	3089.3	3089.3	3088.9
	C2=O9	1758.2	1722.5	1729.1
	C7=O8	1661.1	1629.5	1627.6
	C5=C6	1698.2	1684.7	1683.7
2n	N1-H	3642.5	3635.0	3634.8
	N3-H	3640.8	3632.9	3632.6
	C4-H	3077.0	3080.0	3079.7
	C2=O9	1759.1	1725.9	1724.5
	C7=O8	1646.9	1623.8	1622.3

	C5=C6	1696.2	1682.6	1681.6
2o	N1-H	3643.8	3635.7	3634.9
	N3-H	3641.0	3633.4	3632.8
	C4-H	3078.0	3071.9	3071.8
	C2=O9	1758.1	1725.9	1724.2
	C7=O8	1651.6	1626.0	1624.3
	C5=C6	1699.4	1684.1	1683.0
2p	N1-H	3643.5	3634.6	3634.3
	N3-H	3641.5	3632.5	3632.1
	C4-H	3079.4	3100.6	3100.7
	C2=O9	1758.9	1724.1	1722.7
	C7=O8	1652.5	1630.2	1628.2
	C5=C6	1698.5	1685.1	1684.3

Summary of the results reported that in Table 11 are:

1. These data confirm the results reported in Tables 9 and 10.
2. Confirm the structure of solvation of HHQs (Scheme 2).
3. Frequencies for all functional groups shifted to smaller numbers (Confirm the scheme 2).

Conclusions

We have described an alternative and general method for the multicomponent synthesis of functionalized of some 4-Aryl-1,3,4,6,7,8-hexahydroquinazolin-2,5 (1*H*,6*H*)-diones using nano K_3AlF_6as a basic catalyst. The prospect of the reusability of this catalyst has also been demonstrated without compromising on the yield of the product.(Table 5)On the whole, the protocol presented here is an excellent alternative to many of the reported procedures by the use of nano K_3AlF_6as an environmentally benign and recyclable catalyst. This catalyst can be the decreasing of reaction time is approximately 30-100 minutes.

Zeta potential results show that the interaction of benzaldehyde with the catalyst surface causes increases the relative negative charge on the catalyst surface. Furthermore, the interaction of urea with the catalyst surface makes the more positive charge on the catalyst surface. So, according to the zeta potential data can be suggested a mechanism for this reaction. (Scheme 1)

Analysis of the optimized structures of these compounds by DFT method shows that the heterocyclic ring adopts a boat conformation, flattened at N1 toward an envelope conformation, with a pseudo-axial orientation of the C4 substituent. According to data reported in the NBO theory section, it can be concluded that the resonance share of N3-H to C2=O9 group is more than of N1-H group. Because the E2 (kcal) related to resonance share N3-H→C2=O9 is less than N3-H→C5=C6.So, the N1-H group is more tendentious to resonate with C5=C6 and C7=O8 groups.

The reason for the decrease in the energy band gap in the solution phases of these compounds is related to the formation of hydrogen bonds of water and ethanol with the functional groups of these compounds. (Scheme 2)

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