A Sustainable Synthesis, Eco-Safe Approach Efficiency and DFT Study of Novel 5,6,7,8-Tetrahyroquinazolin-2(1*H*)-one Derivatives as Antioxidant Reagents

Mohammed Abed Kadhim[1], Amin Farouk Mohamed Fahmy[2], Emad Khelil Mohammed Zangana[3*], Aya Ibrahim Hassaballah[2], and Sameh Ahmed Rizk[2]**

[1]*Department of Chemistry, College of Sciences, University of Anbar, Ramadi 55431, Iraq*

[2]*Department of Chemistry, Faculty of Science, Ain Shams University, Cairo 11566, Egypt*

[3]*Department of Chemistry, Faculty of Science and Health, Koya University, Koya KOY45, Iraq*

Corresponding author:

email:
Emad.Zangana@koyauniversity.org; *samehrizk@sci.asu.edu.eg***

Received: April 2, 2023
Accepted: May 11, 2023

DOI: 10.22146/ijc.83583

Abstract: *5,6,7,8-Tetrahydroquinazolin-2-(thio)-ones (THQ) fits the class of* N*-heterocycles as a structural core in numerous bioactive compounds. They promptly extended previous decades. They were significantly recognized in combinatorial chemistry and materials science to determine the drug discovery, antioxidants, and pharmaceuticals fields. In the present work, one-pot multicomponent sustainable synthesis of THQ with easily accessible starting materials, i.e., cyclohexanone, different aromatic aldehydes and (thio)urea, has been performed to determine the proposed Biginelli mechanism that is supported by DFT. It is found that the THQs are synthesized by a mechano-chemical (grinding) tool to achieve a yield of 85.2% within 3.5 min, i.e., YE (% yield/time) 24.34 differs from the conventional method in which lower % yield (YE = 0.72) of THQ was achieved. This confirmed that in the green chemistry principle, the determination of % yield according to saving reaction time must be considered. Moreover, DFT-based antioxidant properties of the THQ were also studied in which the most potent antioxidant compounds were* ***7b*** *>* ***6d*** *>* ***2f****. Softness (σ, eV^{-1}) and hardness (η, eV mol^{-1}) can approve the soft molecule that stays more reactive as a result of decreasing the energy gap along heterocyclic with values 0.1491 > 0.1300 > 0.1168 eV^{-1} one-to-one with the efficiency of antioxidant.*

Keywords: *green chemistry; eco-safe approach efficiency; DFT; antioxidant reagents; 5,6,7,8-tetrahyroquinazolin-2(1*H*)-one*

■ INTRODUCTION

It has been 40 years since Biginelli's initial report was published. The first mechanism for the synthesis of dihydropyrimidinone was conducted by Folkers and Johnson [1], who based their deduction on the reaction yields. Bimolecular condensation of benzaldehyde and urea was suggested as an intermediate in the reaction product. In 1973, a second mechanistic proposal was suggested by Sweet and Fissekis [2], which involved an aldol condensation between benzaldehyde and ethyl acetoacetate to form a stabilized carbonium ion as a primary step. Kappe et al. [3] reinvestigated the mechanism using ^{1}H and ^{13}C-NMR spectroscopy. He established that the acid-catalyzed condensation between aldehyde and urea generated iminium ion **1**. Interception of this iminium ion by ethyl acetoacetate, possibly through its enol tautomer, produces an open chain ureide **2**, which subsequently cyclizes to dihydropyrimidine DHPMs **3** by the removal of H_2O (Scheme 1). Biginelli protocol had a problem with low to moderate yields, mainly when substituted aromatic and aliphatic aldehydes are hired. As a result of various adverse effects, further severe conditions and long reaction times have occurred [4-6].

Recently, expose improved reaction protocols for the synthesis *via* a one-pot approach [7-9] or using novel or complex multistep strategies [10-11]. The efficiency of chemical reactions is determined by atom economy

(AE), which shows the atoms in a reaction's starting components that are incorporated (reaction steps) to obtain the intended output, (i.e., how effectively the reactant atoms are used in a certain reaction. The conversion efficiency is measured by AE and yield economy (YE), which also determine the yield (%) of the desired product at reaction time (yield (%)/reaction time (min)) [12-13].

Based on green chemistry published papers, the authors have shown the significance of the density functional theory (DFT) with multicomponent reactions (MCR) method (YE, AE and RME) in approaching the sustainability of the newly heterocyclic synthesis. It has been reported that 2,2′-azino-bis-(3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt (ABTS) was used to measure the antioxidant activity of pure substances in the presence of hydrogen peroxide (H_2O_2). That method is also appropriate for investigating the water and lipid-soluble antioxidants as well as studying pure substances as reducing antioxidants**.** Adding the antioxidants to the new compound (pre-formed radical cation) decreases its ABTS to a certain level over time, depending on the antioxidant activity, the concentration of the antioxidant, and reaction durations. Thus, the amount of decolorization is assessed as a percentage inhibition of the $ABTS^{\bullet+}$ radical cation, and as a function of concentration and duration, then it is computed relative to the reactivity of ascorbic acid as a standard, under the same circumstances [14-15].

In the present work, we synthesized a new series of 5,6,7,8-tetrahydroquinazolin-2-(thio)-ones, which is supported by DFT, using readily available starting materials such as cyclohexanone, various aromatic aldehydes, and (thio)urea. It has been discovered that the THQs are synthesized using a mechano-chemical (grinding) tool, which results in a yield of 85.2% in 3.5 min, or YE (% yield/time) = 24.34, as opposed to the conventional approach, which produced a lower yield (YE = 0.72) of THQ. Moreover, the most effective antioxidant molecules were **7b** > **6d** > **2f** according to investigations of the THQ's DFT-based antioxidant capabilities, the schematic diagram for this investigation is shown in Fig. 1.

■ EXPERIMENTAL SECTION

Materials

All the chemicals and solvents utilized without additional purification were from Merck, Darmstadt, Germany. These reagents included urea (CH_4N_2O, 99.0%), thiourea (CH_4N_2S, +99%), *N*-phenylurea ($C_7H_8N_2O$, 97%), potassium hydroxide anhydrous (KOH, 99.99%), cyclohexanone ($C_6H_{10}O$, 99.8%), benzaldehyde (C_7H_6, 99.5%), 4-chlorobenzaldehyde (C_7H_5ClO, 97%), 4-nitrobenzaldehyde ($C_7H_5NO_3$, 97%), 4-methoxybenzaldehyde ($C_8H_8O_2$, 98%), 4-(dimethylamino)benzaldehyde ($C_9H_{11}NO$, 98%), hydrochloric acid solution (HCl, 37%), ethanol (99.9%), benzene (99.8%), petroleum ether 60/80, sodium bisulfate ($NaHSO_4$, 99.0%), and hydrogen peroxide (H_2O_2).

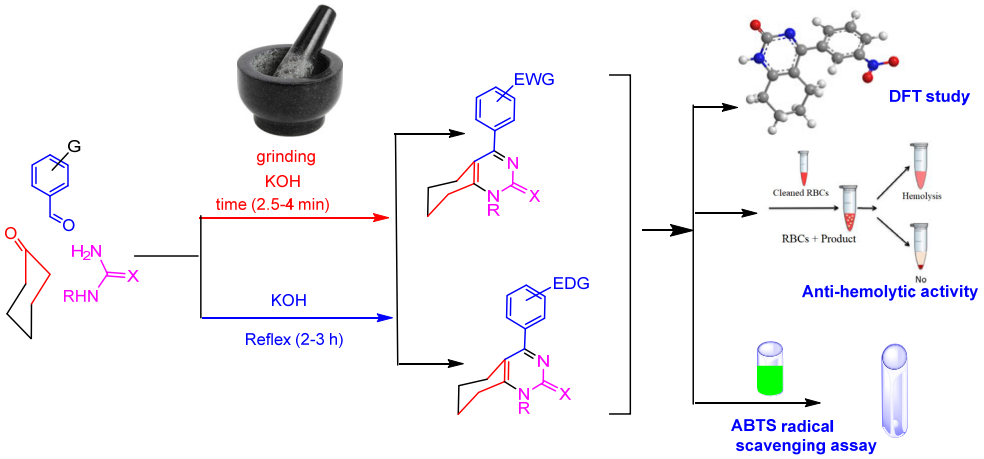


Fig 1. Schematic diagram of this study

Instrumentation

Melting point of the synthesized compounds was measured with Gallen Kamp apparatus (London, UK), and microanalytical data can be seen in Table 1. IR spectra can be verified on a Perkin Elmer RXIFTIR spectrometer (Waltham, USA). A Varian Gemini 300 MHz spectrometer was used to measure the ^{1}H-NMR spectra (Palo Alto, CA, USA) and recorded in DMSO-d_6. The chemical shifts were recorded in δ (ppm) and TMS was used as an internal standard. For the purpose of determining mass, a Tokyo, Japan-based Shimadzu GC-MS spectrophotometry QP 1000 EX system that operates at 70 eV was used. All the reactions were monitored by TLC.

Procedure

*Synthesis of 5,6,7,8-tetrahyroquinazolin-2(1*H*)-ones (THQs)* via *mechanochemical technique*

The mixture of the aromatic aldehydes (3 mmol), cyclohexanone (3 mmol) with binucleophile (3 mmol) as urea, thiourea and phenyl urea in the presence of the catalytic amount of KOH was grained together at the same time, see Table 1. Once the grinding was completed, as monitored by TLC, the mixture of the reaction has been transformed into a colored solid mass that was acidified with cold H_2O/HCl (4:1). The solid product was recovered, filtered out, and recrystallized from the appropriate solvent.

Table 1. Outline physical characterization of the synthesized compounds and the differences in both grinding times and concentrations

Prod.	Time (min.)		M.p. °C	M.F	Elemental Analysis (%)	
No.	G.	Ref.	(solvent recy.)	(M.W.)	Req.	Found
1a	3.5	120	>300 (ethanol)	$C_{14}H_{13}N_2OCl$	C:64.50 H:5.03 N:10.74	C:64.19 H:4.72 N:10.80
1b	3.5	135	180-182 (benzene)	$C_{14}H_{13}N_3O_3$	C:61.99 H:4.83 N:15.49	C:61.52 H:4.56 N:15.27
2a	4.0	150	>300 (ethanol)	$C_{14}H_{14}N_2O$	C:74.31 H:6.24 N:12.38	C:73.90 H:7.12 N:12.40
2b	4.0	150	140–142 (petroleum 60/80)	$C_{15}H_{16}N_2O_2$	C:70.29 H:6.29 N:10.93	C:69.90 H:6.80 N:10.57
2c	4.0	150	234–237 (Ethanol)	$C_{16}H_{19}N_3O$	C:71.35 H:7.11 N:15.60	C:71.12 H:7.59 N15.32
3a	3.5	180	160–162 (Benzene)	$C_{14}H_{13}N_2SCl$	C:60.75 H:4.73 N:10.12	C:60.55 H:5.91 N:10.35
3b	3.5	180	140–142 (Benzene)	$C_{14}H_{13}N_3SO_2$	C:58.52 H:4.56 N:14.62	C:58.78 H:4.77 N:14.52
4a	3.5	180	280–282 (Benzene)	$C_{14}H_{14}N_2S$	C:69.39 H:5.82 N:11.56	C:69.14 H:5.67 N:11.28
4b	3.5	180	136–138 (Benzene)	$C_{15}H_{16}N_2SO$	C:66.15 H:5.92 N:10.29	C:66.39 H:6.13 N:10.25
4c	2.5	120	170–173 (Pet/Benzene)	$C_{16}H_{19}N_3S$	C:67.33 H:6.71 N:14.72	C:66.89 H:7.25 N:14.54

Prod. No.	Time (min.) G.	Time (min.) Ref.	M.p. °C (solvent recy.)	M.F (M.W.)	Elemental Analysis (%) Req.	Found
5a	3.0	120	158–160 (Ethanol)	$C_{20}H_{17}N_2OCl$	C:71.32 H:5.09 N:8.32	C:71.49 H:5.12 N:8.48
5b	3.0	120	134-136 (Ethanol)	$C_{20}H_{17}N_3O_3$	C:69.15 H:4.93 N:12.10	C:68.92 H:5.04 N:12.47
6a	3.0	120	215-217 (Ethanol)	$C_{20}H_{18}N_2O$	C:79.44 H:6.00 N:9.26	C:79.36 H:6.42 N:9.05
6b	3.0	120	224-226 (Benzene)	$C_{21}H_{20}N_2O_2$	C:75.88 H:6.06 N:8.43	C:75.36 H:6.37 H:8.27

Synthesis of 5,6,7,8-tetrahyroquinazolin-2(1H)-ones (THQs)* via *conventional technique

Aromatic aldehydes (3 mmol) dissolved in absolute ethanol (30 mL) and the solution was then refluxed with (3 mmol) of cyclohexanone and (3 mmol) of binucleophile for instance, urea, thiourea and phenyl urea with catalytic amount of KOH for 2–3 h (the reaction was monitored by TLC (ethyl acetate:toluene (2:1)). The reaction mixture was vacuum distilled to half of its volume, and after that, it was acidified with diluted hydrochloric acid (4:1). The identical chemicals were produced by obtaining a solid product, which was filtered and recrystallizing from appropriate solvents.

4-(4-Chlorophenyl)-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (1a). White crystal, IR (ν, cm^{-1}): 3223 (NH), 3034 (ArC–H), 2966 (AliC–H), 1700 (C=O) and 1646 (C=N), MS (*m/z*) [M+2; 55%] 264, [M^+, 100%], 262, 172, 159, 143, 120. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.74–2.06 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 4.07–4.14 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 6.37–6.68 (*m*, 4H, ArH), 10.14 (*s*, 1H, NH, exchangeable D_2O), ^{13}C-NMR (100 MHz, DMSO) δ: 22.28, 43.29, 52.82, 67.78, 128.40, 128.94 (2), 129.14, 129.41 (2), 130.72, 131.37, 132.57 (2), 139.65, 141.42, 153.54, 154.46, 155.96, 169.6., Anal. Calc. for $C_{14}H_{13}N_2OCl$ (260.072), %C:64.50; %H:5.03; %N:10.74 found, %C:64.19; %H:4.72; %N:10.80.

4-(3-Nitrophenyl)-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (1b). White crystal, IR (ν, cm^{-1}): 3432 (NH), 3002 (Arom C–H), 2991 (Aliph C–H), 1679 (C=O), MS (*m/z*) [$M^{+\cdot}$] 272, 265, 253, 240, 212. ^{1}H-NMR (400 MHz, DMSO) δ: 1.82–1.96 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.95–2.99 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 7.38–7.79 (*m*, 4H, ArH), 9.92 (*s*, 1H, NH, exchangeable D_2O), ^{13}C-NMR (100 MHz, DMSO) δ: 22.28, 43.29, 52.82, 67.78, 128.40, 128.94 (2), 129.14, 129.41 (2), 130.72, 131.37, 132.57 (2), 139.65, 141.42, 153.54, 154.46, 155.96, 168.3, Anal. Calc. for $C_{14}H_{13}N_3O_3$ (271.096), %C:61.99; %H:4.83; %N:15.49 found, %C:61.52; %H:4.56; %N:15.27.

4-Phenyl-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (2a). White crystal, IR (ν, cm^{-1}): 3324, (NH), 3062 (ArC–H), 2981 (AliC–H), 1714 (C=O), MS (*m/z*) [$M^{+\cdot}$] 228, 216, 190, 165, 95. ^{1}H-NMR (400 MHz, DMSO) δ: 1.23-1.91 (*m*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.95–2.99 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 7.22–7.50 (*m*, 5H, ArH), 9.51 (*s*, 1H, NH, exchangeable D_2O). Anal. Calc. for $C_{14}H_{14}N_2O$ (226.111), %C:74.31; %H:6.24; %N:12.38 found, %C:73.90; %H:7.12; %N:12.40.

4-(4-Methoxyphenyl)-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (2b). White crystal, IR (ν, cm^{-1}): 3379 (NH), 3032 (ArC–H), 2907 (AliC–H), 1674 (C=O), MS (*m/z*) [$M^{+\cdot}$] 256, 238, 228, 203, 163, 114, 92. ^{1}H-NMR (400 MHz, DMSO) δ: 2.08–2.49 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.95–2.99 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 3.82 (*s*, 3H, OCH_3), 7.02–7.62 (*m*, 4H, ArH), 10.32 (*s*, 1H, NH, exchangeable D_2O). Anal. Calc. for $C_{15}H_{16}N_2O_2$ (256.121), %C:70.29; %H:6.29; %N:10.93 found, %C:69.90; %H:6.80; %N:10.57.

4-(4-(Dimethylamino)phenyl)-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (2c). White crystal, IR (ν, cm^{-1}): 3222 (NH), 3079 (Ar C–H), 2981 (Ali C–H), 1708 (C=O), ^{1}H-NMR (400 MHz, DMSO) δ: 1.01–1.71 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.49–2.52 (*dt*, 4H,

$2CH_2$, *J* = 8.8, 4.9 Hz), 2.95 (*s*, 6H, $N(CH_3)_2$), 6.88–7.29 (*m*, 4H, ArH). Anal. Calc. for $C_{16}H_{19}N_3O$ (269.153), %C:71.35; %H:7.11; %N:15.60 found, %C:71.12; %H:7.59; %N15.32.

4-(4-Chlorophenyl)-5,6,7,8-tetrahydroquinazolin-2(1*H*)-thione (3a). White crystal, IR (ν, cm^{-1}): 3077 (ArC–H), 2979 (AliC–H), MS (*m/z*) [$M^{+\cdot}$+2; 55%] 280, [$M^{+\cdot}$, 100%], 278, 263, 159, 146, 120. ^{1}H-NMR (400 MHz, DMSO) δ: 1.03–1.39 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 7.38–7.79 (*m*, 4H, ArH), Anal. Calc. for $C_{14}H_{13}N_2SCl$ (276.049), %C:60.75; %H:4.73; %N:10.12 found, %C:60.55; %H:5.91; %N:10.35.

4-(3-Nitrophenyl)-5,6,7,8-tetrahydroquinazolin-2(1*H*)-thione (3b). White crystal, IR (ν, cm^{-1}): 3304 N-H, 2836 (SH), 3088 (ArC–H), 2976 (AliC–H). MS (*m/z*) [$M^{+\cdot}$] 289, 284, 255, 240, 221. ^{1}H-NMR (400 MHz, DMSO) δ: 1.01–1.09 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.22–2.30 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 7.38–7.79 (*m*, 4H, ArH), 9.92 (*s*, 1H, NH, exchangeable D_2O), ^{13}C-NMR (100 MHz, DMSO) δ: 22.28, 43.29, 52.82, 67.78, 128.40, 128.94 (2), 129.14, 129.41 (2), 130.72, 131.37, 132.57 (2), 139.65, 141.42, 153.54, 154.46, 165.96. Anal. Calc. for $C_{14}H_{13}N_3SO_2$ (287.073), %C:58.52; %H:4.56; %N:14.62 found, %C:58.78; %H:4.77; %N:14.52.

4-Phenyl-5,6,7,8-tetrahydroquinazoline-2(1*H*)-thione (4a). White crystal, IR (ν, cm^{-1}): 3320 (NH), 3065 (ArC–H), 2956 (AliphC–H), 1614 (C=S), MS (*m/z*) [$M^{+\cdot}$] 239, 224, 209, 190, 165, 95. ^{1}H-NMR (400 MHz, DMSO) δ: 1.33–1.91 (*m*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.95–2.99 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 7.38–7.79 (*m*, 5H, ArH), 8.06 (*s*, 1H, NH, exchangeable D_2O), 8.42 (*s*, 1H, NH, exchangeable D_2O). Anal. Calc. for $C_{14}H_{14}N_2S$ (242.088), %C:69.39; %H:5.82; %N:11.56 found, %C:69.14; %H:5.67; %N:11.28.

4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinazoline-2(1*H*)-thione (4b). White crystal, IR (ν, cm^{-1}): 3266 (NH), 3039 (ArC–H), 2920 (AliC–H), 1407 (C=S), MS (*m/z*) [$M^{+\cdot}$-NH] 260, 251, 224, 210, 142, 112, 90. ^{1}H-NMR (400 MHz, DMSO) δ: 1.91–1.95 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.61–2.57 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 3.43 (*s*, 3H, OCH_3), 7.32–7.45 (*m*, 4H, ArH), 9.27 (*s*, 1H, NH, exchangeable D_2O). Anal. Calc. for $C_{15}H_{16}N_2SO$ (272.098), %C:66.15; %H:5.92; %N:10.29 found, %C:66.39; %H:6.13; %N:10.25.

4-(4-(Dimethylamino)phenyl)-5,6,7,8-tetrahydroquinazoline-2(1*H*)-thione (4c). White crystal, IR (ν, cm^{-1}): 3327 (NH), 3082 (ArC–H), 2930, 2861 (AliC–H), 1395 (C=S), MS (*m/z*) [$M^{+\cdot}$] 282, 280, 217, 185, 151, 144, 110, 96. ^{1}H-NMR (400 MHz, DMSO) δ: 1.07–1.25 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.95–2.95 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 6.63–7.57 (*m*, 4H, ArH), 9.56 (*s*, 1H, NH, exchangeable D_2O). Anal. Calc. for $C_{16}H_{19}N_3S$ (285.13), %C:67.33; %H:6.71; %N:14.72 found, %C:66.89; %H:7.25; %N:14.54.

4-(4-Chlorophenyl)-5,6,7,8-tetrahydro-1-phenylquinazolin-2(1*H*)-one (5a). White crystal, IR (ν, cm^{-1}): 3077 (ArC–H), 2918 (AliC–H), 1664 (C=O), MS (*m/z*) [$M^{+\cdot}$+2; 55%] 338, [$M^{+\cdot}$, 100%] 336, 276, 165, 138, 111. ^{1}H-NMR (400 MHz, DMSO) δ: 1.74–2.06 (*d*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 44.55–4.57 (*d*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 7.38–7.79 (*m*, 9H, ArH), ^{13}C-NMR (100 MHz, DMSO) δ: 22.28, 43.29, 52.82, 67.78, 128.40, 128.94 (2), 129.14, 129.41 (2), 130.72, 131.37, 132.57 (2), 139.65, 141.42, 153.54, 154.46, 155.96, 169.6. Anal. Calc. for $C_{20}H_{17}N_2OCl$ (336.103), %C:71.32; %H:5.09; %N:8.32 found, %C:71.49; %H:5.12; %N:8.48.

4-(3-Nitrophenyl)-5,6,7,8-tetrahydro-1-phenylquinazolin-2(1*H*)-one (5b). White crystal, IR (ν, cm^{-1}): 3088 (ArC–H), 2956 (AliC–H), 1680 (C=O), MS (*m/z*) [$M^{+\cdot}$] 348, 331, 256, 149, 134. ^{1}H-NMR (400 MHz, DMSO) δ: 1.22–1.49 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.95–2.99 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 7.39–7.90 (*m*, 9H, ArH). Anal. Calc. for $C_{20}H_{17}N_3O_3$ (347.127), %C:69.15; %H:4.93; %N:12.10 found, %C:68.92; %H:5.04; %N:12.47.

1,4-Diphenyl-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (6a). White crystal, IR (ν, cm^{-1}): 3062 (ArC–H), 2956 (AliC–H), 1688 (C=O), MS (*m/z*) [$M^{+\cdot}$] 302, 294, 264, 206, 76. ^{1}H-NMR (400 MHz, DMSO) δ: 1.33–1.91 (*m*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 2.95–2.99 (*dt*, 4H, $2CH_2$, *J* = 8.8, 4.9 Hz), 7.38–7.79 (*m*, 9H, ArH). Anal. Calc. for $C_{20}H_{18}N_2O$ (302.142), %C:79.44; %H:6.00; %N:9.26 found, %C:79.36; %H:6.42; %N:9.05.

4-(4-Methoxyphenyl)-1-phenyl-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (6b). White crystal, IR (ν, cm^{-1}): 3059 (ArC–H), 2933 (AliC–H), 1674 (C=O), MS (*m/z*) [$M^{+\cdot}$] 335, 281, 129, 119, 91. ^{1}H-NMR

(400 MHz, DMSO) δ: 1.03–1.21 (*dt*, 4H, $2CH_2$, J = 8.8, 4.9 Hz), 2.27–2.49 (*dt*, 4H, $2CH_2$, J = 8.8, 4.9 Hz), 3.33 (*s*, 3H, OCH_3), 7.13–7.37 (*m*, 9H, ArH). Anal. Calc. for $C_{21}H_{20}N_2O_2$ (332.152), %C:75.88; %H:6.06; %N:8.43 found, %C:75.36; %H:6.37; %N:8.27.

Quantum mechanical calculations

Geometrically optimized using hybrid DFT with Becke 3-parameters exchange potential and L-Y-P correlation functional (B3LYP) theory [16-17] with 6-31 G. Frontier orbitals (FO) indices were calculated in electron volt (eV) for the ligands using Jaguar module of Schrödinger interface [12-13]. For this purpose, the favorable binding poses of the ligand molecules obtained after the docking protocol were subjected to DFT analysis. It was analyzed using frontier molecular orbitals, namely highest occupied molecular orbitals (HOMOs), lowest unoccupied molecular orbitals (LUMOs), and their energy gap difference (HLG). When HOMO energy values show the ability of a ligand molecule to donate electrons, LUMO energies propose the capability of a ligand molecule to accept electrons from the protein. Additionally, the global descriptors for reactivity, such as chemical potential, hardness, electrophilicity, and softness, were analyzed in order to understand the mechanistic aspects of the hits in their ground states.

Antioxidant experiment

Antihemolytic activity. The anti-hemolytic potential of extract/fraction was inspected by a spectrophotometric procedure as described previously [13]. Five milliliters of blood from a healthy person was collected in EDTA vials and centrifuged for 5 min at 1000 × g. The supernatant was removed and the pellet was washed thrice with PBS (0.2 M, pH 7.4) before re-suspending in saline solution (0.5%). A 0.5 mL of the extract/fraction (100–1000 µg/mL in PBS) was dispensed to 1 mL of erythrocyte suspension and incubated at room temperature for 20 min. Next, 0.5 mL of H_2O_2 solution made in buffered saline was added to the reaction mixture to provoke oxidative degradation of the membrane lipids. Subsequently, the samples were centrifuged at 1000 × g for 10 min and the absorbance of supernatant was noted spectrophotometrically at 540 nm. The relative hemolysis was assessed in comparison with the hemolysis in the H_2O_2 treated (negative control), which was set as 100%. For positive control, phosphate buffer saline was used. Each set of experiments was performed in triplicate and the inhibitory activity of different fractions was calculated and expressed as percent inhibition of hemolysis.

ABTS test. The ABTS test has been used to evaluate the antioxidant perspective of all the synthesised compounds. ABTS (7 mM) interacts, in the dark, with potassium persulfate (2.45 mM) for 12 h at room temperature to obtain ABTS radical cations. ABTS solution was then diluted with methanol (50%) to have an absorbance at 745 nm $ABTS^{\bullet+}$ blue/green chromophores [10-12]. Percentage inhibition was calculated by Eq. (1).

$$\text{Quenching ability } (\%) = \frac{\text{control}_{abs} - \text{sample}_{abs}}{\text{control}_{abs}} \times 100 \quad (1)$$

Ascorbic acid was utilized as a standard control.

■ RESULTS AND DISCUSSION

Chemistry

Design and green synthesis

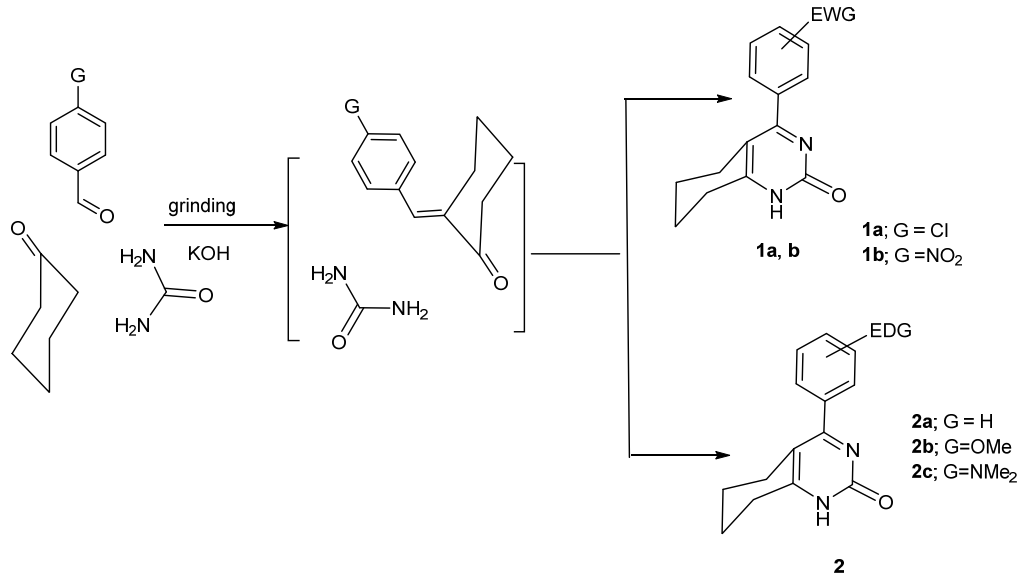
Substituting the *N*-amino group is one of the methods to increase the MCR's adaptability with urea and thiourea moieties which means using semi-carbazide and thiosemicarbazide. Quantum chemical computations explained the efficient one-pot synthesis of 5-aryl-1,3,4-triazaspiro[5.5]undecane-2,7-dione (**1a**, **b**), 3-aryl-2,3,4,5,6,7-hexahydro-1*H*-indazole-1-carboxamide (**2a**-**e**), through treatment aromatic aldehydes, cyclohexanone and carbazides. The proposed mechanism (Scheme 1) has been registered by DFT. The electron-deficient group in the aromatic aldehydes (high electrophilicity index) first attracted the carbazide and then reacted with cyclohexanone to get 1,3,4-triazaspiro[5,5]undecane-2,7-dione (**1**). Lower reactivity of the substituted benzaldehyde carrying electron donated group (higher LUMO) can be preferred to couple with cyclohexanone (soft-soft attack to afford C–C bond formation) for producing the corresponding chalcone which undergoes nucleophilic attacks *via* semi- and thiosemicarbazide followed by cyclization to afford the hexahydro-1*H*-indazole-1-carboxamide derivatives (**2a**-**e**).

THQ has a phenyl ring condensed with pyrimidin-4-one nucleus (Scheme 1). Most of the THQ derivatives are substituted on the carbon 4 chiral center. Therefore, the present article is aimed to apply mechano-chemical MCR *via* grinding for the synthesis of such heterocycles. MCR is a crucial step in the synthesis that helps to confirm the prevalence of this strategy in the target, THQ derivatives **1**, **2**, **3** and **4** (Scheme 1). The reaction of arylidene cyclohexanone *via* Michael reaction sites (N1, C3) is intended to prepare the target compounds (Scheme 2).

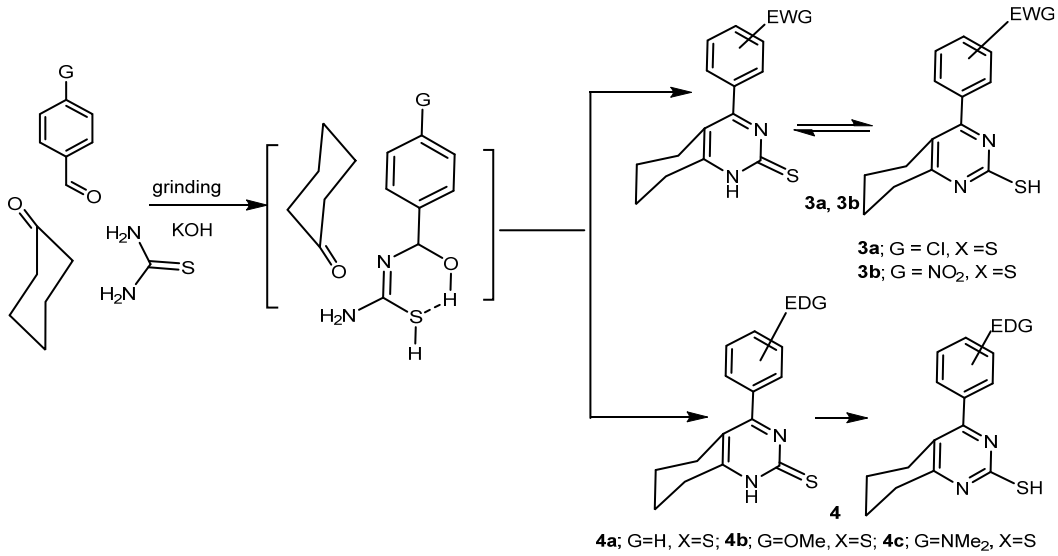
Using a variety of nitrogen nucleophiles, both electron-rich and electron-deficient aldehydes were accepted e.g., urea, thiourea, and phenyl urea in the presence of cyclohexanone (Scheme 3).

Measuring and process efficiency

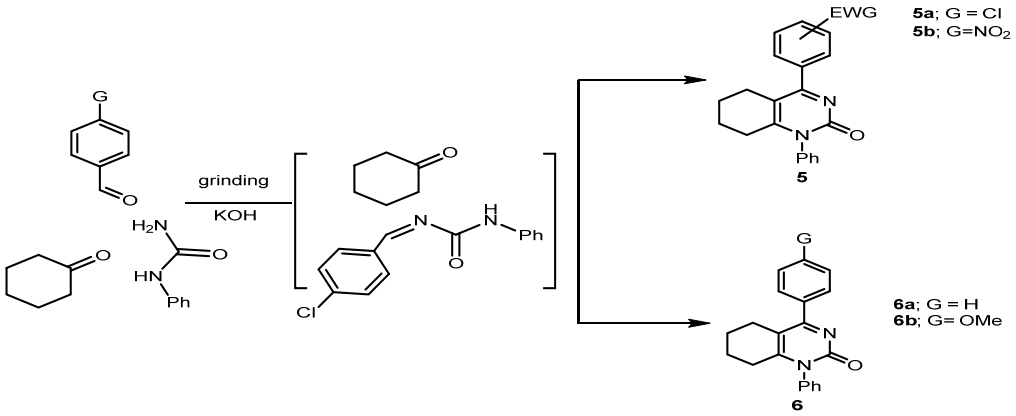
MCRs are broadly defined as "one-pot" processes that connect at least three components simultaneously to enable fast production, such as heterocyclic in a single operation with sufficient chemical diversity from readily available reagents and thus respect the demanding



Scheme 1. Outline MCR of aromatic aldehyde, cyclohexanone and urea *via* mechanochemical method



Scheme 2. Outline MCR of aromatic aldehyde, cyclohexanone and thiourea *via* the mechanochemical method



Scheme 3. Outline MCR of aromatic aldehyde, cyclohexanone and phenyl urea *via* the mechanochemical method

eco-compatibility principle like step efficiency and atom economy [15]. In addition, facile automation, simplicity, higher product yields and minimal waste generation reduce the cost, time, and energy [18]. Because of this, a greater YE suggests a higher degree of conversion, a chemical process that is considerably more effective, and the most cost-effective reaction, as previously said in Table 2. It is found that THQ **1** is synthesized by the mechanochemical (grinding) tool has % yield 85.2 at 3.5 min i.e., YE = 24.34 which differ from the conventional method YE = 0.72. In contrast, the % yield of pyrimidine **1** *via* conventional was greater (see more in Table 2).

Our MCR is used for the synthesis of THQ through a traditional method with regard to their AE [19] to yield identical target substances. As a result, we provided the YE to estimate the percentage yield (%) of the target product. An advanced level of conversion, an effective chemical process, and a cost-effective reaction are all revealed by a greater YE. Hence, 4.86 and 0.08 were the values of YE in the mechanochemical processes, respectively, disclosing the larger status of the former approach and providing conventional conditions and great yield assessment. This confirmed that in the green chemistry principle the determination of % yield according to saving reaction time must be considered.

DFT Study

High E_{HOMO} shows a strong molecule tendency to donate electrons and low values of the energy gap ($\Delta E=E_{LUMO}-E_{HOMO}$), which will render good inhibition efficiencies [16-17]. The structural optimization of the 2-benzylidenecyclohexane-1-one when reacting with urea

Table 2. Outline and description e some physical characteristics. AE (Atom economy), YE (yield economy), and RME (reaction mass efficiency) of the produced compounds

Prod.	Time (min)		Yield (%)		YE (%/min)		AE	RME		O.E (RME/AE)	
No.	Gri.	Refl.	Gri.	Refl.	Gri.	Refl.		Gri.	Refl.	Gri.	Refl.
1a	3.5	120	85.20	86.92	24.34	0.72	87.93	74.83	76.31	86.78	86.78
1b	3.5	135	81.57	82.90	23.30	0.61	87.70	71.42	72.38	81.43	82.53
2a	4.0	150	83.47	81.01	20.86	0.32	86.36	72.11	69.51	83.49	80.48
2b	4.0	150	76.59	78.04	19.14	0.013	87.41	67.22	68.64	76.90	78.52
2c	4.0	150	83.46	81.29	20.86	0.54	87.62	73.16	70.92	83.49	80.94
3a	3.5	180	86.21	86.00	28.73	0.47	90.12	61.53	77.42	68.27	85.90
3b	3.5	180	83.80	82.90	23.94	0.46	90.12	74.74	74.01	82.93	82.12
4a	3.5	180	73.70	75.99	21.05	0.42	91.51	65.31	67.63	71.36	73.90
4b	3.5	180	83.75	81.40	23.92	0.45	90.27	73.40	75.53	81.31	83.67

to produce the desire product is planned by using quantum chemical calculations. In the presence of KOH, the HOMO energy (−9.60 eV) of the cyclohexanone anion was rather than HOMO (−12.61 eV) urea nucleophile and so good matching to LUMO energy (−5.62 eV) of the electrophilic carbonyl site of benzaldehyde to form the corresponding chalcone *via* aldol reaction followed by nucleophilic addition of urea precursor (Fig. 2 and 3). While employing thiourea (Fig. 4), it is preferable to use (HOMO −8.96 eV) rather than HOMO of cyclohexanone anion (−9.60 eV). The presence of benzylidene thiourea intermediate is created by KOH using the technique in Scheme 2.

DFT simulation was assisted to know that MCRs do not occur simultaneously, meaning two components reacted first and combined with a third. The structures have been supported by full spectral analysis and micro-analytical data. Fig. 3 and 4 show the outline reaction steps of the urea cyclohexanone and 3-nitrobenzaldehyde.

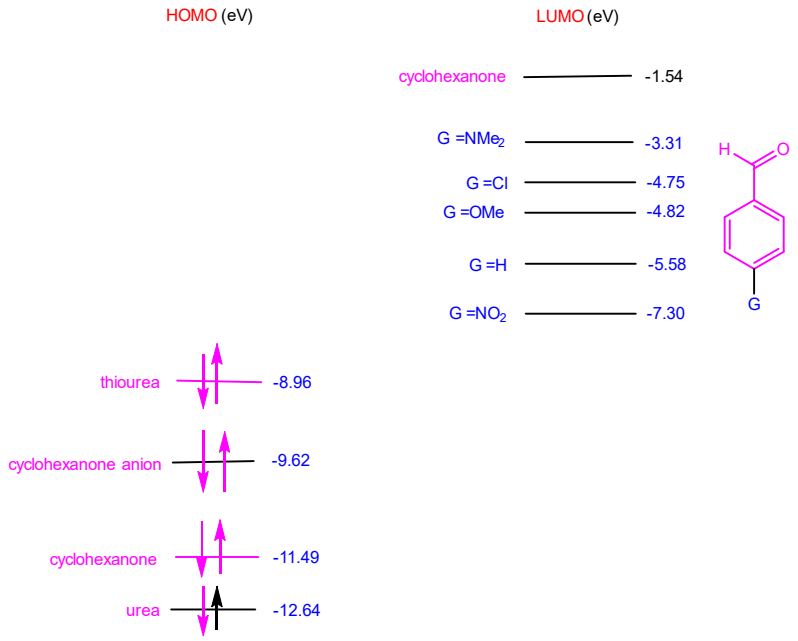


Fig 2. Outline ternary HOMO-LUMO interaction

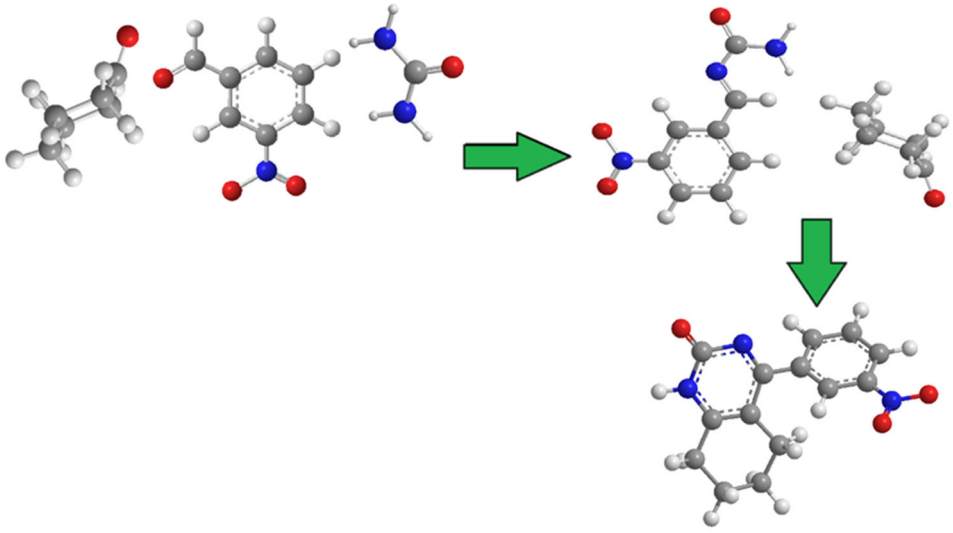


Fig 3. Outline the reaction steps of the urea cyclohexanone and 3-nitrobenzaldehyde

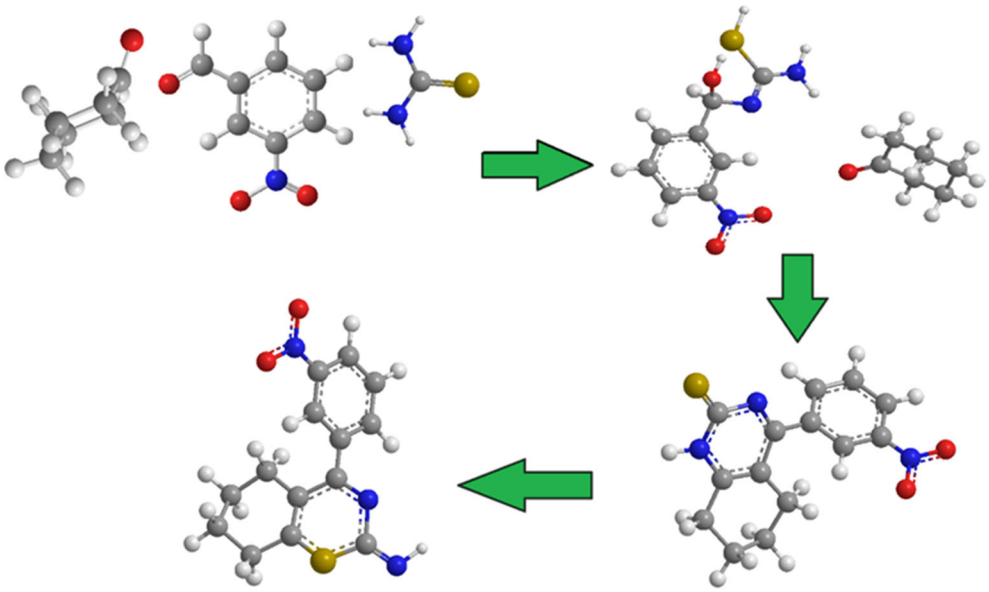


Fig 4. Outline the reaction steps of the thiourea cyclohexanone and 3-nitrobenzaldehyde

On the other hand, the HOMO energy (−10.0 eV) of phenyl urea was in a good overlap with the LUMO energy of benzaldehyde moiety in the absence of KOH because cyclohexanone has HOMO (−11.50 eV) and LUMO (−1.55 eV) besides, the lower basicity of phenyl urea is not sufficient to afford active methylene of cyclohexanone intermediate.

The authentic reaction of the (*Z*)-1-(4-chlorobenzylidene)-3-phenylurea (HOMO −8.25 eV) with LUMO (−1.55 eV) of cyclohexanone afforded the same product **5a**. The presence of KOH in the latter reaction will occur in the same mechanism as Scheme 1 because the HOMO of cyclohexanone anion become higher than the HOMO of phenyl urea. Electron-withdrawing groups of the aromatic aldehydes play an important role in aromatization, orientation and isomerization of the THQ products, see Fig 5.

Quantum chemical computations using DFT method for synthetic chemicals are also well-aligned with the antioxidant efficiency according to calculations (Table 3). The findings show that the gap energy (ΔE) values are quantum chemical computations using DFT method for synthetic chemicals are also well-aligned with the antioxidant efficiency according to calculations (Table 3). The findings show that ΔE values are within the range, where $\Delta E=E_{LUMO}-E_{HOMO}$, following the order: heterocyclic

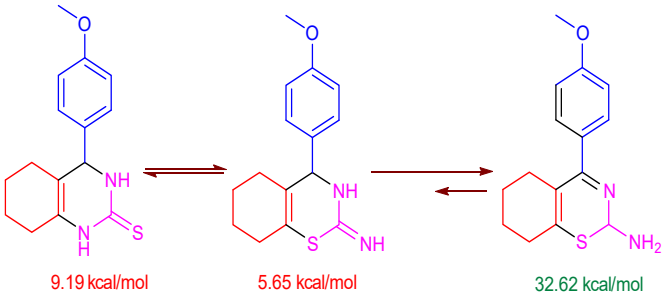


Fig 5. Outline aromatization, orientation and isomerization of the 5,6,7,8-tetrahydroquinazolin-2-one (THQ) derivatives

Table 3. Quantum chemical parameters for the most potent THQ

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	I (eV)	A (eV)	χ (eV)	H (eV)	σ (eV^{-1})	ΔN	μ (Debye)	A_{molec} (nm^2)
2b	−8.57	−5.52	3.01	9.09	0.38	4.74	4.65	0.1068	0.26	8.790	297.443
3b	−8.13	−7.52	0.59	8.88	0.83	4.86	4.03	0.1300	0.34	11.558	542.608
4a	−5.57	−5.20	0.33	8.66	0.66	4.66	4.00	0.1491	0.38	12.139	590.401
Ascorbic acid	−3.47	−2.72	0.75	8.13	1.23	4.69	3.45	0.1281	0.31	9.395	519.866

Table 4. Outline the erythrocyte hemolysis of the synthesized compounds

Entry	Compounds	Erythrocyte hemolysis (A/B × 100)	
		Absorbance of samples (A)	% hemolysis
Absorbance of H_2O (B)		0.850	---
Vit – C		0.031	3.64
1	**1a**	0.043	5.05
2	**1b**	0.043	4.98
3	**2a**	0.048	5.64
4	**2b**	0.026	2.41
5	**2c**	0.042	4.94
6	**3a**	0.044	5.14
7	**3b**	0.037	3.88
8	**4a**	0.018	1.64
9	**4b**	0.044	4.17
10	**4c**	0.051	5.60

Table 5. Outline and an explanation of the synthetic compounds' ability to scavenge ABTS

Entry	Method	ABTS $(Abs_{control}-Abs_{test}/Abs_{control}) \times 100$	
	Compounds	Absorbance of samples	% inhibition
	Control of ABTS	0.525	0
	Ascorbic-acid	0.061	88.4
1	**1a**	0.404	23.0
2	**1b**	0.409	22.1
3	**2a**	0.102	80.1
4	**2b**	0.047	91.5
5	**2c**	0.412	21.5
6	**3a**	0.406	22.7
7	**3b**	0.408	22.3
8	**4a**	0.035	97.8
9	**4b**	0.163	71.7
10	**4c**	0.410	21.9

derivatives **3b** < **4a** < ascorbic acid < **2b**. When a chemical has a low ΔE value, it is more reactive to surface interactions with radicals i.e., easy electron donation to the surface of a hole [20-21]. Furthermore, the great correlation, including the number and type of heteroatoms, dipole moment, electron distributions, softness (σ, eV^{-1}), and surface area (nm^2), between oxidation inhibition effectiveness and THQ-carrying hydrophobic groups were approved. Ionization potential is another factor (I, eV), and charge density distribution (ΔN) shows the greatest amount of electron transport and, hence, a stronger propensity to scavenge the radicals.

Antioxidant Assays

Anti-hemolytic activity

It was hoped to synthesize THQ derivatives which incorporate a hydrophobic group would have improved properties, such as the inhibitory activity of the opioid receptor and antioxidant characteristics. The fully optimized minimum energy geometrical configuration of the most potent antioxidant compounds **2b**, **3b** and **4a** have been approved**.** The significant antioxidant

activity of such compounds was corroborated by the findings of DFT-based anti-hemolytic and radical scavenger experimental tests. The results indicated that compounds **1b**, **2a**, **2b**, **3b**, **4a**, **4b**, and **4c** exhibited potent anti-hemolytic action (Table 4). It has been demonstrated that when extract or fraction concentration increases, erythrocyte lysis decreases [22]. The findings from this investigation indicate that primary antioxidants exist and have an antihemolytic effect. percentage of hemolysis is increased along heterocyclic compounds **1b** < **2a** < **4b** < **3b** < ascorbic acid (3.64%) < **2b** < **4a** that matched with the DFT study.

ABTS radical scavenging assay

The attained result nominated THQ **2b** and **4a** to scavenge the ABTS radicals. THQ **2b** (98.0 ± 0.1 µg/mL) has the lowest EC-50 values for radical ABTS scavenging while compound **4a** (> 500 ± 0.26 µg/mL) was the highest EC-50 values as shown in Table 5. % Inhibition decreases in order to these synthetic heterocyclic derivatives **4a** > **2b** > ascorbic acid (61 ± 0.2 µg/mL) > **2a** > **4b** that roughly corroborated the findings of antihemolytic and their DFT investigation.

■ CONCLUSION

The current work examines the synthesis and antioxidant properties of novel 5,6,7,8-tetrahyroquinazolin-2(1*H*)-one derivative for the first time. The two-step, straightforward, innovative, and environmentally friendly synthetic methods were used to create the novel 5,6,7,8-tetrahyroquinazolin-2(1*H*)-one derivative. Grinding and reflux techniques were compared in terms of time, yields, and reactions. All synthetic compounds' complete structural elucidations were based on spectroscopic and elemental investigations, including FTIR, mass, and ^{1}H-NMR. All products underwent insecticidal assessments. When using the ABTS test to evaluate the antioxidant perspective, compounds **2a**, **2b**, **4a**, and **4b** in particular, have shown much stronger inhibition than the other examined compounds. By using these new molecules, antioxidants are able to recognize and scavenge free radicals *in vivo* as well as *in vitro*. They will be promising as a therapeutic candidate for avoiding the onset and spread of several illnesses. This will pave the way for the synthesis of quinazolinone derivatives with maximum hydrophobicity and antioxidant activity in the near future through employing pyrimidine derivatives. The outcomes of DFT-based anti-hemolytic and radical scavenger experimental testing confirmed the considerable antioxidant activity of such substances. Compounds **1b**, **2a**, **2b**, **3b**, **4a**, **4b**, and **4c** were shown to have significant anti-hemolytic activity. Moreover, DFT-based bioassay of such compounds that had higher introduction of where $E=E_{LUMO}-E_{HOMO}$, follows the order: heterocyclic derivatives **3b** < **4a** < ascorbic acid < **2b** than the other examined compounds.

■ ACKNOWLEDGMENTS

The authors would like to extend their sincere appreciation to the organic laboratory, Department of Chemistry, Faculty of Science of Ain Shams University and STDF under call number 37139. Also, appreciation for both Departments of Chemistry in Collage of Sciences, University of Anbar, and Faculty of Science and Health, Koya University.

■ REFERENCES

[1] Folkers, K., and Johnson, T.B., 1933, Researches on pyrimidines. CXXXVI. The mechanism of formation of tetrahydropyrimidines by the Biginelli reaction[1], *J. Am. Chem. Soc.*, 55 (9), 3784–3791.

[2] Sweet, F., and Fissekis, J.D., 1973, Synthesis of 3,4-dihydro-2(1*H*)-pyrimidinones and the mechanism of the Biginelli reaction, *J. Am. Chem. Soc.*, 95 (26), 8741–8749.

[3] Kappe, C.O., Fabian, W.M.F., and Semones, M.A., 1997, Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators. A comparison of ab initio, semiempirical and X-ray crystallographic studies, *Tetrahedron*, 53 (8), 2803–2816.

[4] Chen, R., Singh, P., Su, S., Kocalar, S., Wang, X., Mandava, N., Venkatesan, S., Ferguson, A., Rao, A., Le, E., Rojas, C., and Njoo, E., 2022, Benchtop ^{19}F nuclear magnetic resonance (NMR) spectroscopy provides mechanistic insight into the Biginelli

condensation towards the chemical synthesis of novel trifluorinated dihydro- and tetrahydropyrimidines as antiproliferative agents, *ACS Omega*, 8 (11), 10545–10554.

[5] Balraj, G., Rammohan, K., Anilkumar, A., Sharath Babu, M., and Ayodhya, D., 2023, An improved eco-friendly and solvent-free method for the one-pot synthesis of tetrahydropyrimidine derivatives *via* Biginelli condensation reaction using ZrO_2/La_2O_3 catalysts, *Results Chem.*, 5, 100691.

[6] Fu, R., Yang, Y., Lai, W., Ma, Y., Chen, Z., Zhou, J., Chai, W., Wang, Q., and Yuan, R., 2015, Efficient and green microwave-assisted multicomponent Biginelli reaction for the synthesis of dihydropyrimidinones catalyzed by heteropolyanion-based ionic liquids under solvent-free conditions, *Synth. Commun.*, 45 (4), 467–477.

[7] Fiorito, S., Genovese, S., Curini, M., Preziuso, F., Taddeo, V.A., and Epifano, F., 2017, Ytterbium triflate promoted solvent-free synthesis of 2-amino-4*H*-pyranes, *Tetrahedron Lett.*, 58 (16), 1659–1661.

[8] Bochevarov, A.D., Harder, E., Hughes, T.F., Greenwood, J.R., Braden, D.A., Philipp, D.M., Rinaldo, D., Halls, M.D., Zhang, J., and Friesner, R.A., 2013, Jaguar: A high-performance quantum chemistry software program with strengths in life and materials sciences, *Int. J. Quantum Chem.*, 113 (18), 2110–2142.

[9] Cao, M., Wang, S., Gao, Y., Pan, X., Wang, X., Deng, R., and Liu, P., 2020, Study on physicochemical properties and antioxidant activity of polysaccharides from *Desmodesmus armatus*, *J. Food Biochem.*, 44 (7), e13243.

[10] EL-Hashash, M., Rizk, S.A., El-Bassiouny, F., Guirguis, D., Khairy, S., and Guirguis, L., 2017, Facile synthesis and structural characterization of some phthalazin-1(2*H*)-one derivatives as antimicrobial nucleosides and reactive dye, *Egypt. J. Chem.*, 60 (3), 407–420.

[11] Shutalev, A.D., Kishko, E.A., Sivova, N.V., and Kuznetsov, A.Y., 1998, A new convenient synthesis of 5-acyl-1,2,3,4-tetrahydropyrimidine-2-thiones/ones, *Molecules*, 3 (3), 100–106.

[12] Abdalrazaq, E., Jbarah, A.A.Q., Al-Noor, T.H., Shinain, G.T., and Jawad, M.M., 2022, Synthesis, DFT calculations, DNA interaction, and antimicrobial studies of some mixed ligand complexes of oxalic acid and Schiff base trimethoprim with various metal ions, *Indones. J. Chem.*, 22 (5), 1348–1364.

[13] Fahmy, A.F.M., El-Sayed, A.A., and Hemdan, M.M., 2016, Multicomponent synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones (azlactones) using a mechanochemical approach, *Chem. Cent. J.*, 10 (1), 59.

[14] Al-Atbi, H.S., Al-Assadi, I.J., Al-Salami, B.K., and Badr, S.Q., 2020, Study of new azo-azomethine derivatives of sulfanilamide: Synthesis, characterization, spectroscopic, antimicrobial, antioxidant and anticancer activity, *Biochem. Cell. Arch.*, 20 (2), 4161–4174.

[15] Al-Khazragie, Z.K., Al-Salami, B.K., and Al-Fartosy, A.J.M., 2022, Synthesis, antimicrobial, antioxidant, toxicity and anticancer activity of a new azetidinone, thiazolidinone and selenazolidinone derivatives based on sulfonamide, *Indones. J. Chem.*, 22 (4), 979–1001.

[16] Bursavich, M.G., Parker, D.P., Willardsen, J.A., Gao, Z.H., Davis, T., Ostanin, K., Robinson, R., Peterson, A., Cimbora, D.M., Zhu, J.F., and Richards, B., 2010, 2-Anilino-4-aryl-1,3-thiazole inhibitors of valosin-containing protein (VCP or p97), *Bioorg. Med. Chem. Lett.*, 20 (5), 1677–1679.

[17] Imai, S., Kikui, H., Moriyama, K., and Togo, H., 2015, One-pot preparation of 2,5-disubstituted and 2,4,5-trisubstituted oxazoles from aromatic ketones with molecular iodine, oxone, and trifluoromethanesulfonic acid in nitriles, *Tetrahedron*, 71 (33), 5267–5274.

[18] Rizk, S.A., and Shaban, S., 2019, A facile one-pot synthesis and anticancer evaluation of interesting pyrazole and pyrimidinthione *via* heterocyclic interconversion, *J. Heterocycl. Chem.*, 56 (9), 2379–2388.

[19] El-Hashash, M.A., and Rizk, S.A., 2016, Regioselective diastereomeric Michael adducts as

building blocks in heterocyclic synthesis, *J. Heterocycl. Chem.*, 53 (4), 1236–1240.

[20] Akanni, O.O., Owumi, S.E., and Adaramoye, O.A., 2014, *In vitro* studies to assess the antioxidative, radical scavenging and arginase inhibitory potentials of extracts from *Artocarpus altilis*, *Ficus exasperate* and *Kigelia africana*, *Asian Pac. J. Trop. Biomed.*, 4, S492–S499.

[21] Yahyazadeh, A., Nafei-Kohi, M., Abbaspour-Gilandeh, E., and Aghaei-Hashjin, M., 2022, A new procedure for the preparation of 3,4-dihydropyrimidin-2(1*H*)-one and octahydroquinazolinone derivatives catalyzed by SCMNPs@CA-EASO$_3$H under solvent-free conditions, *Lett. Org. Chem.*, 19 (10), 867–883.

[22] Puripat, M., Ramozzi, R., Hatanaka, M., Parasuk, W., Parasuk, V., and Morokuma, K., 2015, The Biginelli reaction is a urea-catalyzed organocatalytic multicomponent reaction, *J. Org. Chem.*, 80 (14), 6959–6967.