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One-Pot Synthesis of 7, 7-Dimethyl-4-Phenyl-2-Thioxo-2,3,4,6,7, 8-Hexahydro-1H-Quinazoline-5-OnesUsing Zinc Ferrite Nanocatalyst and Its Bio Evaluation

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Abstract: A simple and highly efficient protocol for the synthesis of derivatives 7, 7-dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazoline-5-one from 5, 5-dimethyl cyclohexane-1, 3-dione (**4a**–**4h**) (dimedone) has been described. The aryl aldehydes were substituted with thiourea in the presence of synthesized zinc ferrite nanocatalyst, which increased the yield under reflux through condensation, followed by cyclization to give desired products. The other advantages are that it is eco-friendly and economically affordable for large-scale production. Structural validation and characterization of all the newly synthesized compounds were evaluated by spectral analysis (mass spectrometry, proton nuclear magnetic resonance (^{1}HNMR), and Carbon-13 nuclear magnetic resonance(^{13}CNMR)spectroscopies. The structure of antibacterial and antifungal assays was performed with the newly synthesized compounds. The antimicrobial activity of title compounds possessing electron-withdrawing groups such as (**4e**–**4h**) (Cl, Br, and cyano group) exhibited more active potential than the electron-donating groups, C_6H_5,4-C_6H_4, 3-OC_2H_5-4OH-C_6H_3, etc., (**4a**–**4d**) containing moiety.

Keywords: dimedone; aryl aldehydes; zinc ferrite; bio evaluation; structural validation; NMR

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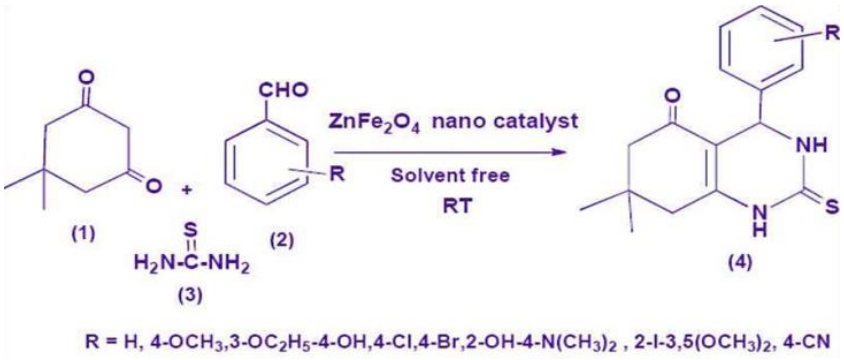
1. Introduction

Multicomponent reaction (MCR) is the most powerful and efficient technique in modern synthetic organic chemistry. The advantages of these reactions in synthetic organic chemistry are the valuable characteristics such as constructing desired compounds, straightforward reaction design, atom economy, and the simple purification of target products. MCRs with heterocyclic moiety are particularly useful for the construction of drug-like molecules [1–3]. In the recent past, the six-membered heterocyclic compounds such as hexahydroquinazolinones in medicinal chemistry and synthetic organic chemistry are of special interest. The main focus on the synthesis of derivatives of 7,7-dimethyl-4-phenyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quinazoline-5-ones has considerably attracted

attention in recent years due to their potential, antioxidant [4], antifungal, antibacterial, antitumor, and antitubercular activity [5] with wide applications, including anticonvulsant, sedative, tranquilizer, analgesic [6,7], antimicrobial, anesthetic [8], anticancer [9], antihypertensive [10], anti-inflammatory [11], diuretic [12], and muscle relaxant properties [13]. The various organic transformation reactions were employed by the use of trimethylsilyl chloride [14]. There are few reports for the synthesis of octa hydro quinazolinone derivatives using catalysts such as concentrated H_2SO_4 [15], Nafion-H [16], NH_4VO_3 [17], silica-sulfuric acid [18], and also in ionic liquids [HMIM] H_2SO_4 in presence of TMSCl [19], [BMIM]Br-[BMIM]BF_4 [20], and $ZrOCl_2$. $8H_2O$ [21]. This article tends to report the synthesis of 7, 7-dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones using nanocatalyst. Lanthanum doped Ni0.6Zn0.2Fe2-XLaXO4 (x = 0.075) ferrite was developed by Amol et al. This ferrite has a spinal cubic structure and a lattice constant of 8.486. The Ferro-spinal sample was used as a magnetically recoverable heterogeneous catalyst [22]. Triethanolamine has a significant impact on the morphology of nano-ZnO catalyst. For the synthesis of coumarin derivatives, we developed an efficient, simple, and environmentally friendly synthetic methodology [23]. Catalytic reactions ensure high regio- and stereoselectivity of chemical transformations. In recent years, several novel catalytic systems were developed for the selective formation of carbon–heteroatom and carbon–carbon bonds [24]. The use of green nanocatalyst for the synthesis of various heterocycles has advantages such as short reaction time, high yield, inexpensive chemical usage, easy work-up procedure, and specific reaction [25]. The Michael addition reaction and cyclodehydration, followed by dimedone with various substituted aryl aldehydes and thioureain the presence of nanocatalystgive 7,7-dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-ones, were performed (Scheme 1). A pilot reaction using substituted aryl aldehyde (1), dimedone (2), and thiourea (3) in the presence of nanocatalyst and the structure and antagonistic properties of the synthesized compounds were also studied, in addition to studying the further development of derivatives.



Scheme 1. Synthesisof 7, 7-dimethyl-4-phenyl-2-thioxo-2, 3,4,6,7, 8-hexahydro-1H-quinazolin-5-ones using zinc ferrite.

2. Results

2.1. XRD Pattern of $ZnFe_2O_4$ NPs

The X-ray diffraction (XRD) pattern of $ZnFe_2O_4$(Figure 1) shows clear diffraction peaks. The diffraction peak of the powder sample was indexed according to Joint Committee on Powder Diffraction Standards (JCPDS) card no. 22-1012. The material crystallized in a cubic unit cell with space group Fd-3m(Figure 2). The structure was refined by the Rietveld refinement method with the Fullprof software package using the single-phase Fd-3m diffraction data. The unit cell parameters (Table 1) of the crystallite size of the sample were calculated from the most intense diffraction by using Scherrer's formula. The Scherrer method (using full width at half maximum (FWHM)) calculates the ratio of the thickness's root-mean-fourthpower to its root-mean-square value. We illustrated that the Scherrer equation's calculation of crystallite size is accurate by comparing it to X-ray

diffraction peaks produced by the dynamical theory. In terms of crystalline size and Bragg angle, we also established the range of validity of the acceptable Scherrer equation.

$$D = \frac{K\lambda}{\beta cos\theta}, \quad (1)$$

where K is dimensionless shape factor and generally taken 0.94 for spherical particles, λ is the wavelength of X-ray used ($Cu - K_\alpha$ = 1.540 Å), and β and θ are the full widths of half maxima and diffraction angle of corresponding diffraction peak.

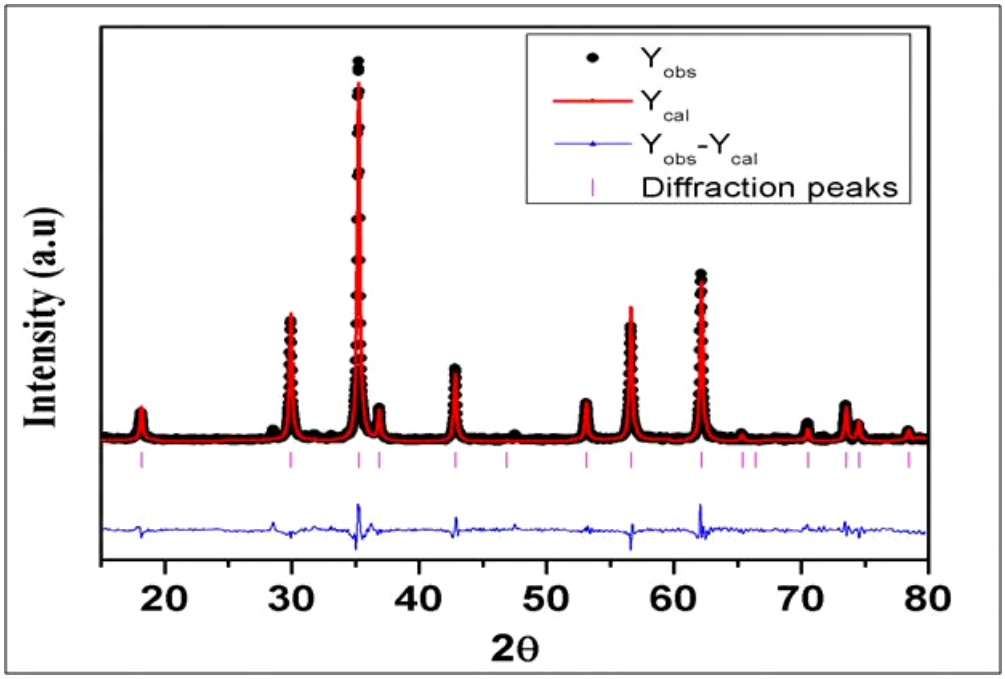


Figure 1. X-ray diffraction (XRD) pattern of ZnFe2O4 NPs.

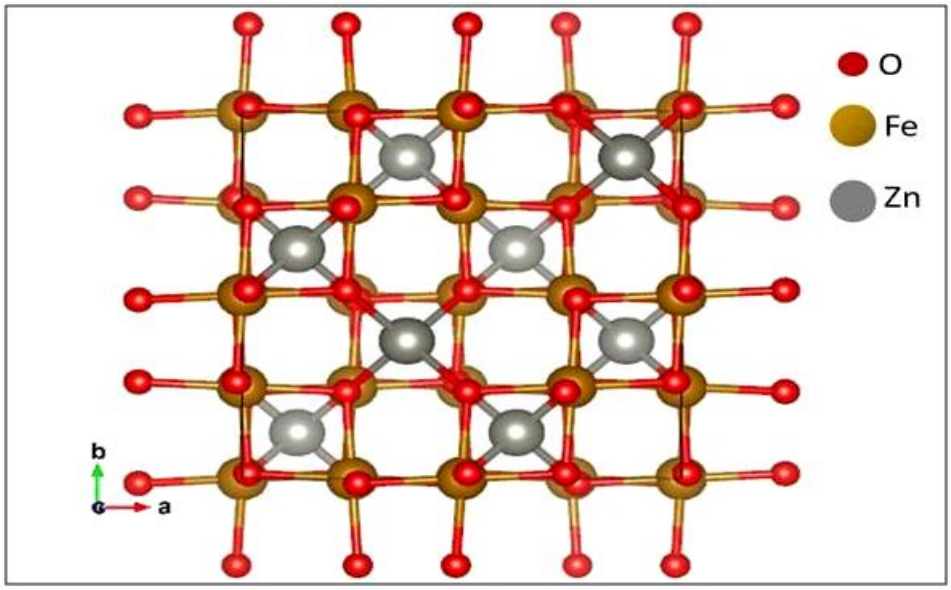


Figure 2. Crystalized in a cubic unit cell of $ZnFe_2O_4$ NPs.

Table 1. Refined unit cells parameters of $ZnFe_2O_4$ nanoparticles.

Atom	x	y	z	Occ.	B_{iso}	Site	Sym.
Zn	0.125	0.125	0.125	1	0.024	8a	43 m
Fe	0.5	0.5	0.5	1.035	0.009	16d	3 m
O	0.26335	0.26335	0.26335	1.038	0.016	32e	3 m
Unit cell Parameters	a = b = c = 8.43695 Å α = β = γ = 90°						
Unit cell Volume	600.559 $Å^3$						
R_p (%)	12.1						
R_{wp} (%)	18.3						
χ^2	2.02						
Fe-O	2.00295 Å						
Zn-O	2.02174 Å						

The average crystallite size of the powder sample was estimated in the close approximation of 39.16 nm. The difference between the calculated and observed data in the Rietveld refinement method elucidates the goodness of fit (χ^2) of the diffraction pattern. The minimal χ^2 value achieved for the synthesized $ZnFe_2O_4$ sample was 2.02, which is implicit in the observed XRD pattern. The lower χ^2 of refined XRD pattern indicates the single-phase and high purity of prepared $ZnFe_2O_4$ nanoparticles.

2.2. SEM Analysis of $ZnFe_2O_4$ NPs

The surface morphology of the acquired $ZnFe_2O_4$ (NPs) was documented using a scanning electron microscope (FESEM) (Figure 3). The FESEM image indicated that the $ZnFe_2O_4$ (NPs) have a smooth surface, and the agglomeration of NPs is also visible there.

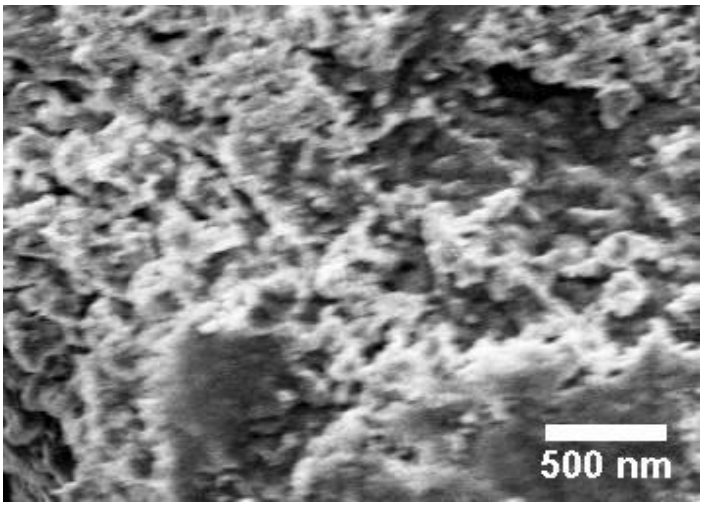


Figure 3. Field emission scanning electron microscopy (FESEM) image of $ZnFe_2O_4$ NPs.

2.3. HRTEM Analysis of $ZnFe_2O_4$ Nano Composite

The high-resolution transmission electron microscopy (HRTEM) images of $ZnFe_2O_4$ (NPs) are shown (Figure 4). The figure indicates that $ZnFe_2O_4$ NPs are uniform and cylindrical. The average particle size was calculated using Image-J software and the particle size is ranged about 50 nm.

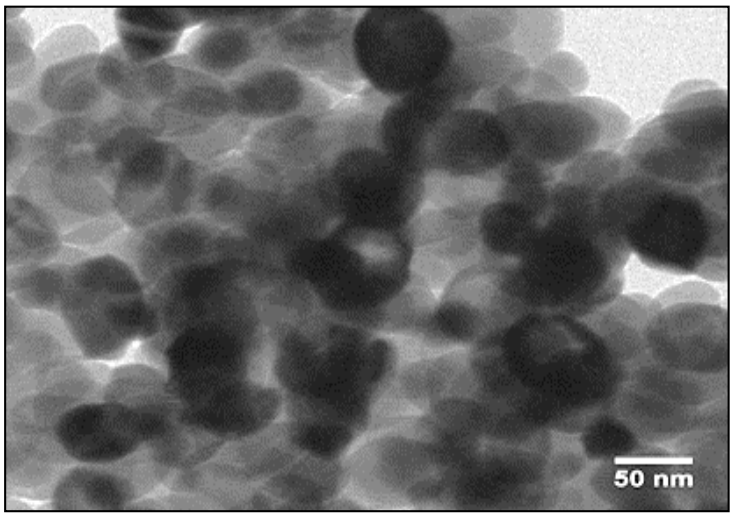


Figure 4. HRTEM Image of $ZnFe_2O_4$ NPs.

2.4. EDS Analysis of $ZnFe_2O_4$ NPs

The elemental composition of $ZnFe_2O_4$ NPs was studied by energy-dispersive X-ray spectroscopy (EDS), as shown in Figure 5. The $ZnFe_2O_4$ NPs exhibit three elemental peaks—one for zinc element located at 1.1 keV, one for oxygen element located at 0.5 keV, and two for iron element located at 0.65 and 6.4 keV. From the EDS data, the weight ratio of Zn:Fe:O is around 43.91:13.97:42.12. The sample consists of only O, Fe, and Znelements.

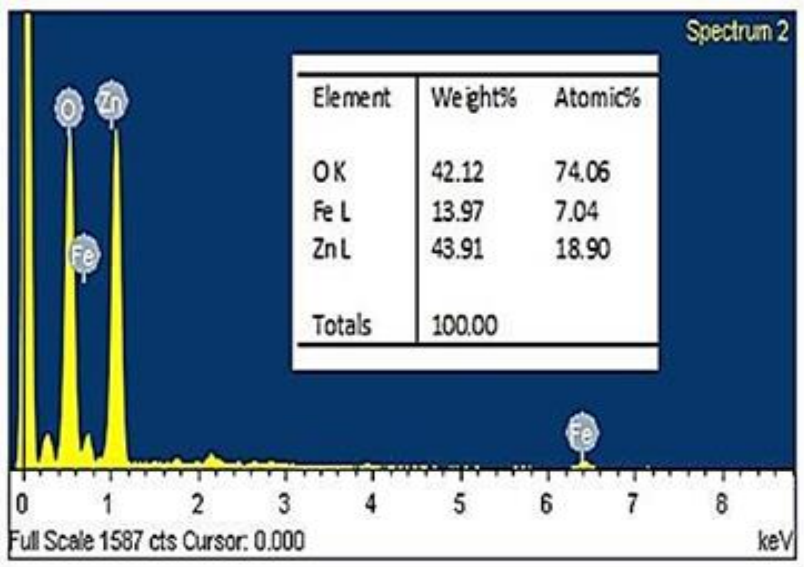


Figure 5. Energy-dispersive X-ray spectroscopy (EDS) pattern $ZnFe_2O_4$ nanoparticles.

2.5. Mass Spectra of Synthesized Compounds

The mass spectrum of **4a** revealed a molecular ion peak at m/z 286, which is consistent with the formula weight (285). This result confirmed the identity of the structure of **4a**. Similarly, the mass spectra of other compounds are also consistent with the proposed structures (for **4d**, m/z = 321, **4g**, m/z= 472 and **4h**, m/z= 310) (Figures S1–S4),

2.6. NMR Spectral Analysis

The ^{1}HNMR spectra of the compounds 7, 7-dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-one from 5, 5-dimethyl cyclohexane-1, 3-diones (**4a**, **4d**, **4g**, **4h**) (Figures S5–S8) were assigned based on the observed chemical shift and relative

intensities of the signals. The ^{1}HNMR spectra of the compounds displayed sharp singlets owing to the two –NH protons in each compound at 9.52–10.36 ppm. ^{1}HNMR spectral values of –NH groups in quinazolones nucleus showed down fields, namely,10.23, 10.13, 10.29, 10.34 ppm (halogens and cyano group). The –NH-groups of quinazolones containing electron donating group (EDG) showed the ^{1}HNMR values in the upfield region such as 9.58, 9.73, 9.54, 9.74, 9.72, 9.84, and 9.52 ppm and also the showed–OH group at 10.24 ppm. The derivatives were obtained by the cyclization with the thiourea added. The two methyl group protons of the compounds fell at 0.92–1.15 ppm. A singlet at 3.57 ppm and a broad singlet at 3.66 ppm for **4b** and **4f** accounts for protons of *p*-methoxy (–OCH_3) and dimethoxy (3,5-OCH_3) groups, respectively. In the case of **4c** and **4d**, the hydroxy (–OH) protons were observed as singlets at 9.33 and 10.24 ppm, respectively. A singlet appeared at 2.74 ppm due to the N–Me proton in **4d**. The resonances due to aryl ring protons appeared in the range of 6.70–7.56 ppm. The quintets in 2.14–3.46 ppm and singlet around 2.40 ppm corresponded to methylene protons of dimedone ring.

The ^{13}CNMR spectra revealed the presence of the expected number of signals corresponding to different types of carbon atoms present in the compounds. The –OCH_3group absorbs at 55.25 (**4g**) and 55.30 (**4h**) ppm slightly downfield to the methyl group carbon due to the deshielding of the directly attached electronegative oxygen atom. The spectra of the compounds exhibit a strong band at 169.8–174.2 ppm and are assigned as C=S group. The ^{13}CNMR display signals in the range 112.4–151.7 ppm, which has been assigned to the aromatic carbon atoms. The signals due to the C attached to the methyl group resonate at 141.4–147.8 ppm. The resonance arising from the carbon attached to the hydroxyl (**4a** and **4d**) group is observed at 158.4 and 158.6 ppm, respectively. Values of downfield (195.2 ppm) compared with other groups (Figures S9–S12).

2.7. Antibacterial Activity

The antibacterial and antifungal activity of **4f**(4-(4-bromophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one) molecule showed high active potentials such as 20, 14,21,22,24 25 mm of inhibition, compared with **4e**(4-(4-chlorophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one) and **4g** (4-(2-iodo-3,5-dimethoxy phenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazoline-5(6H)-one)molecules, which are also better than other compounds (Table 2). We observed that the important result in the investigation of the reaction of substituted aryl aldehydes, 5,5-dimethyl cyclohexane-1,3-dione(dimedone), and thiourea in the presence of nanocatalyst under solvent-free conditions at room temperature (Scheme 1).The advantages of using this catalyst for the reaction, which is responsible for easy work-up, include a short reaction time. Moderate-to-good yields, and purification of title compound by non-chromatographic methods. It is also identified that various substituted aryl aldehydes containing electron-withdrawing and electron-releasing substituents in para-positions lead better yield than ortho substituents. Therefore, we observed that the reaction of aryl aldehydes having an electron-withdrawing group was having a faster rate of reaction, compared to the reaction of aldehydes possessing electron releasing groups. In this reaction, halogen-substituted aryl aldehydes obtain a better yield than the electron-donating group containing aryl aldehyde. The reusability of this catalyst was investigated. The antimicrobial activity of title compounds possessing-electron withdrawing group (EWG) such as (**4e**–**4h**) (halogens and cyano group) exhibited more active potential than the EDG(**4a**–**4d**) containing moiety (Table 3).

Table 2. Synthesis of titled derivatives catalyzed by nanocatalyst solvent-free condition.

Entry	Ar(a)	Molecular Formula	Time [a] (min)	Yield [b] (%)	Molecular Weight (MW) g/mol	m.p (°C) Lit).
4a	C_6H_5	$C_{16}H_{18}N_2OS$	75	85	286.71	285–286 °C
4b	4-OH-C_6H_4	$C_{17}H_{20}N_2O_2$ S	130	87	317.53	274–276 °C
4c	3-OC_2H_5-4-OH-C_6H_3	$C_{18}H_{22}N_2O_3$ S.	150	87	365.22 (M-H).	273–274 °C
4d	4-Cl-C6H4	$C_{16}H_{17}ClN_2OS$	120	90	321.64	274–276 °C (Lit275–276 °C)
4e	4-Br-C_6H_4	$C_{16}H_{17}BrN_2OS$	120	91	366.16	284 °C
4f	2-OH-4-N$(CH_3)_2$-C_6H_3	$C_{18}H_{23}N_3O_2$ S	130	88	345.48	275–277 °C
4g	2-I-3,5-$(OCH_3)_2$-C_6H_3	$C_{18}H_{21}IN_2O_3$S.	150	90	472.29	275–276 °C
4h	4-CN-C_6H_4	$C_{17}H_{17}N_3OS$.	175	88	310.45 (M-H).	269–271 °C

[a] Reaction was continued until the Thin Layer Chromatography (TLC)shown the starting materials disappeared. [b] Isolated yield.

Table 3. In vitro antibacterial and antifungal screening study of the title compounds **4a**–**4h**.

S.No	Compound Code	Zone of Inhibition (mm)					
		Gram-Negative Bacteria		Gram-Positive Bacteria		Fungal Strains	
		E.coli	*P.aeruginosa*	*B.subtilis*	*B.megaterium*	*A.niger*	*C.albicans*
1	**4a**	16	13	21	15	15	16
2	**4b**	14	12	22	14	12	14
3	**4c**	16	15	14	16	13	16
4	**4d**	11	15	15	14	14	15
5	**4e**	19	17	20	20	23	24
6	**4f**	20	14	21	22	24	25
7	**4g**	19	20	21	21	23	24
8	**4h**	17	16	17	18	19	20
Control	**DMSO**		10			10	
Standard	**Streptomycin**	25	25	25	25		
	Fluconazole					30	30

3. Discussion

Dimedone also called 5, 5-dimethylcyclohexane-1, 3-dione is a cyclic diketone, which is used as a key sample molecule for the synthesis of the various moiety in synthetic organic chemistry. These are white to light yellow crystals in color and also have other names such asdimedone, Cyclomethicone, 5, 5-dimethyl-1,3-cyclohexanedione, dimethyl-dihydro resorcinol, and Methone. The molecular formula is $C_8H_{12}O_2$, and its molecular weight is 140.17968 g/mol with a melting point of 147–150 °C (420–423 K). It is stable under ambient conditions and soluble in organic solvents ($CHCl_3$, CC_4, toluene, etc.,) and in methanol, ethanol, and water. One-step reduction of dimedone to 3, 3-dimethylcyclohexanone compound with a yield of 69–73% (98–99% purity) by using Pd-catalyzed medium-pressure dimedone hydrogenation (1) in a solvent mixture of concentrated H_2SO_4 and propionic acid [26] was made. Dimedone and its derivatives have been previously documented to have various biological properties such as anticarcinogenic [27], antioxidant [28], antihistamine [29], and anticoagulant [30]. A three-component one-pot reaction of dimedone, 1, 3-cyclohexanedione, aromatic aldehydes, and malononitrile in the presence of D, L-proline under solvent-free conditions at ambient temperature to produce 2-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7 8-tetrahydrobenzopyrans has been reported [31].

The reaction proceeded at room temperature clearly shows to provide good yields for the products (ae = 94%). An efficient one-pot synthesis of 4H-benzopyrans via a three-component cyclo condensation of malononitrile using $CeCl_3 \cdot 7H_2O$ (10 mol percent) as a catalyst in a 1:2 mixture of water/ethanol under reflux conditions that yielded 70–94% within 1–2 h [32]. Sadehet al. (2017) [33] reported that in most organic transformations, dimedoneis a flexible and fascinating moiety. A wide variety of organic reactions, including one-pot multi-step syntheses, used the white to light yellow crystals of dimedone as a substrate. Dimedone has acidic properties in its methylene group, which is in harmony with its tautomericenol shape, making it possible to use them in various organic reactions. They are also used to evaluate the efficiency of some organic molecules, which have active pharmaceutical properties. Low-cost processing, ease of handling, low toxicity, easy accessibility, and moisture stability made it fascinating for use by synthetic organic chemists. Dimedone was concentrated in much of the reaction with a view to the media solvent. The temperature of the transformations in each segment has been subdivided, and this is used to achieve an organic transition based on green chemistry.

Leoa and Maryam (2018) [34] reported that the key peaks assigned to 200, 311, 400, 422, and 511 and Bragg reflection at 2 θ value of 27.36°, 36.03°, 46.18°, 56.77°, and 62.95° are according to the typical pattern for spinel-structured crystalline magnetite. The average nanoparticle diameter was around 73 nm, estimated from Debye–Scherrer's equation. It is also concluded that the chemical alteration process has not changed the magnetic nanoparticles' crystal structure, diameter, and structure. SEM images of $ZnFe_3O_4$ nanoparticles and $ZnFe_3O_4$@MSA were submitted. Fe_3O_4nano particles have a mean size of approximately 75 nm with good distribution according to SEM images. The SEM picture of Fe_3O_4@MSA shows that, due to the particle size of modified magnetite nanoparticles, the methane sulfonic acid layer attached to the nanoparticle surface is very thin because it is not larger than raw Fe_3O_4. These findings are in line with XRD trends [30].

Antibacterial activity was documented by Appaniet al. [35]. Electron withdrawing groups were demonstrated to have better behavior over aliphatic substituents among the various substituents on the C-2. Compounds with electron withdrawal substituents such as –Cl and–F showed increased activity over unsubstituted and electron releasing substituted moieties. As the most active compounds of the sequence, compounds 9a and 9h appeared to have the most potent activity against *P. Vulgaris* and *B*. Dimedone could be prepared from diethyl malonate and mesityl oxide, which is a safe compound with no or fewer hazards during usage. This dimedone is in equilibrium with its tautomericenol form in chloroform and the hydrogen bonding between the enolic structure results in the crystalline appearance. Dimedone and its analogs have been previously well documented with a wide spectrum of biological properties such as anticarcinogenic, antioxidant, antihistaminic, and anticoagulant [36].

The chemiluminescence property observed during the oxidation process belongs to 4-peroxydimedone radicals that are being synthesized from the first step of oxidation. Other applications of dimedone are colorimetry, crystallography, luminescence, and spectrophotometric analysis. Different types of reactions that include dimedone as a substrate have been presented and are classified based on the reaction media used. This is due to the importance of economical and green transformations in organic synthesis. The reaction could occur under solvent-free conditions, in aqueous media, and in the presence of various organic solvents. Some cases required heat to enhance them, and some others have taken place at room temperature. The above-discussed multiple properties of dimedone create a strong interest for utilizing them in different reactions by the synthetic chemists [37].

4. Materials and Methods

4.1. Materials

All the reagents, chemicals, and solvents (Merck, Mumbai, India) were procured and the melting points of the newly synthesized compounds were determined by using Agrawal 535 melting point apparatus. All the reactions were checked by thin-layer chromatography

using ethyl acetate and n-hexane (5:5) performed on percolated silica gel (Merck, Mumbai, India). The ^{1}HNMR spectra of these compounds were recorded on BRUKER 400 MHz spectrometers and ^{13}CNMR were recorded on BRUKER 100 MHz using $CDCl_3$ as the solvent and Tetramethylsilane as an internal standard. The molecular weight of compounds was determined by mass spectrometry.

4.2. Methods

4.2.1. Preparation of $ZnFe_2O_4$Nanoparticles (NPs)

The nanoparticles of zinc ferrite were prepared using both sol–gel techniques. As precursors, iron nitrate [$Fe(NO_3)_3 \cdot 9H_2O$] and zinc nitrate [$Zn(NO_3)_2 \cdot 6H_2O$] were used.

The precursors were dissolved in 50 mL ethylene glycol aliquot ($C_2H_6O_2$) and then agitated at room temperature for 2 h using a magnetic bead to form a homogenized aqueous solution (0.1 M). To evaporate all the material, the solution was dried for 6 h at 130 °C. Finally, the dry powder was annealed for crystallization at 500 °C for 1 h in the air.

4.2.2. Structural Characterization

The XRD profile at room temperature of the synthesized $ZnFe_2O_4$ (NPs) was obtained. The crystal structure and phase purity of the sample were evaluated, and the crystalline size was determined using the Debye–Scherrer equation. $ZnFe_2O_4$ (NPs) surface morphology was analyzed using the scanning electron microscope (SEM) (TESCAN, CZ/MIRA I LMH). Transmission electron microscope (TEM) (FEI, TECNAIG2TF20-ST) measured the particle size, and the elements present were analyzed by the energy dispersive x-ray analysis (EDS).

4.2.3. General Procedure for the Synthesis of 7, 7-Dimethyl-4-Phenyl-2-Thioxo-2, 3, 4, 6, 7, 8-Hexahydro-1H-Quinazolin-5-One

A mixture of substituted aryl aldehydes (1) (10 mmol), 5,5-dimethyl cyclohexane-1,3-dione(dimedone)(2) (10 mmol) and/thiourea (3) (15 mmol) with the nanocatalyst without solvent taken in a beaker (capacity 50 mL).The total mixture fitted on magnetic stirrer and reaction was proceeding. The completion of the reaction was monitored by TLC (ethyl acetate/hexane (5:5). The reaction mixture was then extracted with ethyl acetate and the catalyst was separated by the filtration. The organic layer was then washed with water and dried over anhydrous Na_2CO_3. The organic solvent was evaporated under reduced pressure and the solid compound was crystallized from absolute ethanol to lead the pure corresponding 7, 7-dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-azones and its derivatives (**4a**–**4h**) in good yields.

7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-one (**4a**):^{1}HNMR (400 MHz, CDCl3), δ ppm:1.02(s, 3H, CMe);1.11(s, 3H, CMe); 2.25 (q, *J* = 16.0 Hz, 2H, CH2); 2.31(s, 2H, CH2); 4.95 (d, *J* = 3.5 Hz,1H, CH); 7.12–7.32 (m, 5H, Ar); 9.66(s, 1H, NH); 10.22(s, 1H, NH); ^{13}CNMR (100 MHz, CDCl3): δ ppm: 193.7, 173.7, 147.8, 141.5, 128.9, 127.6, 125.8, 102.4, 51.5, 49.8, 32.6, 28.0, 26.4.

4-(4-Methoxyphenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (**4b**): ^{1}HNMR (400 MHz, CDCl3), δ ppm: 0.95(s, 3H, CMe); 1.11(s, 3H, CMe); 2.18(q, *J* = 16.2 Hz, 2H, CH2); 3.01(s, 2H, CH2); 3.57(s, 3H, OCH3), 5.10(d, *J* = 2.7 Hz, 1H, CH); 6.82(d, *J* = 8.4 Hz, 2H, Ar); 7.22(d, *J* = 8.8 Hz, 2H, Ar); 9.58(s, 1H, NH); 9.86(s,1H, NH); ^{13}CNMR (100 MHz, CDCl3): δppm: 193.4, 174.0, 158.2, 147.8,137.1,128.8,115.2,107.7, 100.8, 55.9, 52.4, 50.4, 32.9, 28.9, 26.8.

4-(3-ethoxy-4-hydroxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (**4c**): ^{1}HNMR (400 MHz, CDCl3) δppm: 0.97(s, 3H, CMe); 1.11(s, 3H, CMe);1.25(t,3H,CH3); 3.46(q,2H,-CH2-), 2.22(q, =16.1 Hz, 2H, CH2); 2.39(s, 2H, CH2); 4.22(d, *J* = 3.6 Hz, 1H, CH); 6.70–7.51(m,34H, Ar); 9.33(s,1H,-OH); 9.73(s, 1H, NH); 9.94(s, 1H, NH); ^{13}CNMR (100 MHz, CDCl3): δppm:192.9,172.6,158.4,147.8,145.3,139.8,132.5,119.6,116.3,115.5,101.4, 60.9,50.4,47.8,36.9,30.6,26.3,13.7.

4-(4-Dimethylamino)-2-hydroxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quinazolin-5(6H)-one (**4d**): ^{1}HNMR (400 MHz,CDCl3) δppm: 1.05(s,3H,CMe); 1.15(s, 3H, CMe); 2.26(q, *J* = 16.2 Hz, 2H, CH2); 2.36(s, 2H, CH2); 2.74(s, 6H, NMe2), 4.94(d, *J* = 2.6 Hz, 1H, CH); 7.09–7.29 (m, 3H, Ar);9.15(s, 1H, NH);10.02(s,1H,-OH), 9.45(s, 1H, NH); ^{13}CNMR (100 MHz, CDCl3): δppm 193.9,174.2,158.6,151.6,149.2,131.4,126.7,122.9, 121.4,120.5,49.8,46.3, 38.6, 28.8, 26.9.

4-(4-Chlorophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (**4e**): ^{1}HNMR (400 MHz, CDCl3)δppm: 0.94(s, 3H, CMe); 1.05(s, 3H, CMe); 2.19 (q, *J* = 16.5 Hz, 2H, CH2);2.40(s,2H,CH2);5.17(d, *J* = 3.6 Hz,1H,CH);7.36–7.15(m,4H,Ar);9.74(s,1H,NH);10.34(s,1H, NH); ^{13}CNMR(100 MHz,CDCl3) δppm: 194.5,174.2, 150.7, 141.4, 132.0, 129.7, 128.3, 127.4, 125.8, 104.4, 52.8, 50.6, 32.7, 28.9, 25.6.

4-(4-Bromophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (**4f**): ^{1}HNMR (400 MHz, CDCl3) δppm: 0.98(s, 3H, CMe); 1.09(s, 3H, CMe); 2.14(q, *J* = 16.2 Hz, 2H, CH2); 2.35(s, 2H, CH2); 5.08(d, *J* = 2.7 Hz, 1H, CH); 7.20 (d, *J* = 8.4 Hz, 2H, Ar); 7.44(s, *J* = 7.6 Hz, 2H, Ar); 9.72(s, 1H, NH); 10.23(s, 1H, NH); ^{13}CNMR (100 MHz,CDCl3): δ 195.1, 173.6, 147.4, 141.7, 132.7, 130.2, 128.8, 121.5, 104.6, 52.0, 49.2, 32.4, 28.6, 25.9.

4-(2-iodo-3,5-dimethoxy phenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolne-5(6H)-one(**4g**):^{1}HNMR (400 MHz, CDCl3) δ ppm: 0.92(s, 3H, CMe); 1.13(s, 3H, CMe); 2.24(q, *J* = 16.4 Hz, 2H, CH2); 2.84(s, 2H, CH2); 3.66(s, 6H, (2OCH3), 5.07(d, *J* = 2.8 Hz, 1H, CH); 6.872(s, 1H, Ar); 7.02(s, 1H, Ar); 9.84(s, 1H, NH); 10.13(s, 1H, NH); 13CNMR (100 MHz, CDCl3): δppm: 194.6, 169.8, 156.7,151.7, 147.2, 119.8, 116.6, 115.3, 105.4,55.2,54.8, 51.3,48.7, 38.3, 28.6, 25.3. 8)4-(7,7-dimethyl-5-oxo-2-thioxo-1,2,3,4,7,8-ocatahydroquinazolne-4-yl) benzonitrile(**4h**) (400 MHz,CDCl3)δppm: 1.07(s,3H,CMe); 1.16(s, 3H, CMe); 2.32(q, *J* = 16.2 Hz, 2H, CH2); 2.43(s, 2H, CH2); 5.02(d, *J* = 2.8 Hz, 1H, CH); 7.39–7.56 (m, 4H, Ar);9.52(s,1H,NH); 10.29(s,1H,NH);^{13}CNMR(100 MHz,CDCl3)δppm:195.2,173.9,159.5,149.2,145.4,130.6,128.2, 120.8,112.4,104.7,52.3,49.2,38.6,29.4,29.4.

4.2.4. AntimicrobialAssays

Theantimicrobial activity of the titled compounds namely:7,7-dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-ones and its derivatives have been in vitro screened with both bacterial and fungal strains:

Gram-negative—*Escherichia coli, Pseudomonas aeruginosa*;

Gram-positive—*Bacillus subtilisin, Bacillus megaterium*;

Fungal strains—*Aspergillusniger and Candida albicans*.

The synthesized compounds were laid using agar plates containing nutrient broth for bacteria in vitro activities [8–11]. The antibacterial streptomycin and fluconazole were used as standards for antibacterial and antifungal assays, respectively. Dimethyl sulfoxide (DMSO) was used as solvent control. The antimicrobial inhibitions of test compounds were expressed as a zone of inhibition in standard units (mm). This marked antibacterial activity may be due to the presence of high hydrophobic content of this family of compounds and the quinazoline ring system. The compounds containing the quinazalone segment are more active against bacteria due to the strong interaction of the latter with the agar medium; this hinders their diffusion in the agar medium.

5. Conclusions

In conclusion, an efficient nanocatalyst is used for the synthesis of a series of7,7-dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-ones. The present methodology has very attractive features such as reduced reaction times and moderate-to-good yields, and the product was isolated efficiently. We believe that conducting this procedure in solvent-free conditions, along with easy recovery and reuse of catalyst, makethis method environmentally and economically valuable. Thederivativesof7, 7-dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones have biological and medicinal significance.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11040431/s1, Figure S1. Mass spectrum of 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-one (**4a**); Figure S2. Mass spectrum of 4-(4-Dimethylamino)-2-hydroxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,6,7,8-exahydro-1H-quinazolin-5(6H)-one (**4d**); Figure S3. Mass spectrum of 4-(2-iodo-3,5-dimethoxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolne -5(6H)-one(**4g**); Figure S4. Mass spectrum of 4-(7,7-dimethyl-5-oxo-2-thioxo-1,2,3,4,7,8-ocatahydroquinazolne-4-yl) benzonitrile(**4h**); Figure S5. 1H NMR Spectrum of 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-one (**4a**); Figure S6. 1H NMR Spectrum of 4-(4-Dimethylamino)-2-hydroxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,6,7,8-exahydro-1H-quinazolin-5(6H)-one (**4d**); Figure S7. 1H NMR Spectrum of 4-(2-iodo-3,5-dimethoxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolne-5(6H)-one(**4g**); Figure S8. 1H NMR Spectrum of 4-(7,7-dimethyl-5-oxo-2-thioxo-1,2,3,4,7,8-ocatahydroquinazolne-4-yl) benzonitrile(**4h**); Figure S9. 13C NMR Spectrum of 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-one (**4a**); Figure S10. 13C NMR Spectrum of 4-(4-Dimethylamino)-2-hydroxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,6,7,8-exahydro-1H-quinazolin-5(6H)-one (**4d**); Figure S11. 13C NMR Spectrum of 4-(2-iodo-3,5-dimethoxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolne-5(6H)-one(**4g**); Figure S12. 13C NMR Spectrum of 4-(7,7-dimethyl-5-oxo-2-thioxo-1,2,3,4,7,8-ocatahydroquinazolne-4-yl) benzonitrile(**4h**).

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References

1. Lednicer, D.; Mitscher, L.A. *The Organic Chemistry of Drug Synthesis*; Wiley InterscienceSPubl: New York, NY, USA, 1977; Volume 1, pp. 338–342.
2. Lednicer, D.; Mitscher, L.A. *The Organic Chemistry of Drug Synthesis*; Wiley InterscienceSPubl: New York, NY, USA, 1980; Volume 2, p. 361.
3. Kershaw, S.; Stables, J.P.; Jatav, V.; Mishra, P. Synthesis and CNS depressant activity of some derivatives of novel 3-[5-substituted-1, 3,4-thiadiazole-2-yl]-2-styrylquinazolin-4-(3H)-one. *Eur. J. Med. Chem.* **2008**, *43*, 135–141.
4. Sayed, R.E.; Wasfy, A.F. Synthesis of heterocycles having double character: As antimicrobial. *J. Chinesechem. Soc.* **2005**, *52*, 129–135.
5. Tyagi, M.; Pathak, U.S.; Rathod, R.S. Synthesis of 3-monosubstitutedquinazolin-4-(3H)-ones. *Ind. J. Chem.* **1995**, *2*, 617–623.
6. Thierry, B.A.; Jerome, G.; Charles, W.R. Multistepsynthesis of thiazoloquinazolines-under microwave irradiation in solution. *Tetrahedron Lett.* **2020**, *41*, 1027–1030.
7. Bahl, B.S.; Bahl, A.A. *Text Book of Organic Chemistry*; Chand and Company Ltd.: New Delhi, India, 1997; Volume 14, p. 735.
8. Guiry, P.J.; Connolly, D.J.; Cusack, D. Synthesis of quinazolinones and quinazoline. *Tetrahedron* **2005**, *737*, 10153–10202.
9. Feng, L.; Meng, Q.; Feng, Y. An efficient construction of Quinazoline-4-(3H)-ones under microwave irradiation. *ARKIVOC* **2007**, *I*, 40–50.
10. Meyyanathan, S. ASEAN review of biodiversity and environmental conversation. *ABEC* **1998**, *2*, 4–10.
11. Alexandra, P.B.; Thierry, B.; Corinne, F. Diaryliodoniums Salts as Coupling Partners for Transition-Metal Catalyzed C- and N-Arylation of Heteroarenes. *Catalysts.* **2000**, *10*, 1–34.
12. Lidstrom, P.; Tierney, J.; Westman, J. Microwaveassistedorganic synthesis—A review. *Tetrahedron* **2001**, *57*, 9225–9283. [CrossRef]
13. Lottie, B.; Thomas, H. Microwave enhanced decarboxylation of aromatic carboxylic acid, improved potential. *J. Chem. Res.* **2000**, *2*, 42–46.
14. Canevari, S.; Bantu, R.; Nagarapu, L. TMSCl mediated highly efficient one-pot synthesis of octa hydro quinazolinone and 1,8-dioxo-octa hydro xanthene derivatives. *Arkivoc* **2006**, *XVI*, 136–148.
15. Hassani, Z.; Islami, M.R.; Kalantari, M. An efficient one-pot synthesis of octa hydro quinazolinone derivatives using a catalytic amount of H_2SO_4 in the water. *Bioorganic Med. Chem. Lett.* **2006**, *16*, 4479. [CrossRef] [PubMed]
16. Lin, H.; Zhao, Q.; Xu, B.; Wang, X. Nafion-H catalysed cyclocondensation reaction for the synthesis of octa hydro quinazolinone derivatives. *J. Mol. Catal. A: Chem.* **2007**, *268*, 1–2. [CrossRef]
17. Niralwad, K.S.; Shingate, B.; Shingare, M.S. Microwave-assisted one-pot synthesis of octa hydro quinazolinone derivatives using ammonium metavanadate under solvent-free condition. *Tetrahedron Lett.* **2010**, *51*, 3616. [CrossRef]

18. Mobinikhaledi, A.; Foroughifar, N.; Khodaei, H. Synthesis of octa hydro quinazolinone-derivatives using silica sulfuric acid as an efficient catalyst. *Eur. J.Chem.* **2010**, *1*, 291. [CrossRef]
19. Kefayati, H.; Asghari, F.; Khanjanian, R. 1-Methylimidazolium hydrogen sulfate/chlorotrimethylsilane: An effective catalytic system for the synthesis of 3, 4-dihydropyridine-2(1H)-ones and hydroquinazolinone-2,5-diones. *J. Mol. Liq.* **2012**, *172*, 147. [CrossRef]
20. Khurana, J.M.; Kumar, S. Ionic liquids: An efficient and recyclable medium for the synthesis of octa hydro quinazolinone and biscoumarin derivatives. *Montashefte Fur Chem.* **2010**, *141*, 561. [CrossRef]
21. Karami, S.; Karami, B.; Khodabakhshi, S. Solvent-free synthesis of novel and known octahydroquinazolinones/thione by the use of $ZrOCl_2.8H_2O$ as a highly efficient and reusable catalyst. *J. Chin. Chem.Soc.* **2013**, *60*, 22. [CrossRef]
22. Pachpinde, A.M.; Langade, M.M. A simple one pot synthesis of 5-Acetyl-3,4-Dihydro-4-Phenylpyrimidin-2(1H)-one, by using magnetically recoverable heterogeneous nickel substituted nanoferro-spinel catalyst. *Int. J. Res. Appl. Sci. Biotechnol.* **2019**, *6*, 23–26. [CrossRef]
23. Kumar, B.V.; Naik, H.S.B.; Girija, D. ZnO nanoparticle as catalyst for efficient green one-pot synthesis of coumarins through Knoevenagel condensation. *J. Chem. Sci.* **2011**, *123*, 615–621. [CrossRef]
24. Beletskaya, I.; Tyurin, V. Recyclable Nanostructured Catalytic Systems in Modern Environmentally Friendly Organic Synthesis. *Molecules* **2010**, *15*, 4792–4814. [CrossRef]
25. Hemalatha, K.; Madhumitha, G.; Kajbafvala, A.; Anupama, N.; Sompalle, R.; Roopan, S.M. Function of nanocatalyst in chemistry of organic compounds revolution: An overview. *J. Nanomater.* **2013**, *2013*, 1–23. [CrossRef]
26. Cormier, R.A. A convenient synthesis of 3,3-dimethylcyclohexanone. *Synth. Commun.* **1981**, *11*, 295–298. [CrossRef]
27. Singletary, K.; MacDonald, C.; Iovinelli, M.; Fisher, C.; Wallig, M. Effect of the β-diketonesdiferuloylmethane (curcumin) and dibenzoylmethane on rat mammary DNA adducts and tumors induced by 7,12-dimethylbenz[a] anthracene. *Carcinogenesis* **1998**, *19*, 1039–1043. [CrossRef]
28. Rasmussen, H.B.; Christensene, S.B.; Kirs, L.P.; Karazmi, A. A simple and efficient separation of the curcumins, the antiprotozoal constituents of Curcuma longa. *Planta Med.* **2000**, *66*, 396–397. [CrossRef] [PubMed]
29. Matsuzaki, T.; Koiwai, A. Antioxidative-Diketones in stigma lipids of tobacco. *Agric. Biol. Chem.* **1988**, *52*, 2341–2342. [CrossRef]
30. Francis, L.E.; Douglas, D.E. Some observations on the antihistamine activity in the guinea pig of aliphatic 2,4diketones, a new class of physiological tissue components. *Res. Commun. Chem. Patel. Pharmacol.* **1977**, *17*, 357–364.
31. Guo, S.B.; Wang, S.X.; Li, J.T.D. L-Proline-catalyzed one-pot synthesis of Pyrans and Pyrano[2,3c]Pyrazole derivatives by a grinding method under solvent, free conditions. *Synth. Commun.* **2007**, *37*, 2111–2120. [CrossRef]
32. Sabitha, G.; Arundhathi, K.; Sudhakar, K.; Sastry, B.S.; Yadav, J.S. A concise study on dimedone: A versatile molecule in multicomponent reactions, an outlook to the green reaction media. *Synth. Commun.* **2009**, *39*, 433–440. [CrossRef]
33. Sadeh, F.N.; Fatahpour, M.; Hazeri, N.; Maghsoodlou, M.T.; Lashkari, M. One-pot condensation approach for the synthesis of some 1,8-dioxooctahydroxanthenes and 14-aryl-14hdibenzo[a,j]xanthenes using lactic acid as an efficient and eco-friendly catalyst. *Acta Chem. Iasi.* **2017**, *25*, 24–37. [CrossRef]
34. Leila, M.; Maryam, T. Green synthesis of 3,4-dihydropyrimidinones using nanoFe3O4@meglumine sulfonic acid as a new efficient solid acid catalyst under microwave irradiation. *J. Saudi Chem. Soc.* **2018**, *22*, 66–75.
35. Ramgopal, A.; Baburao, B.; Kiran, G. *Synthesis and Antibacterial Activity of 3-(Substituted)-2-(4-oxo2-Phenylquinazolin-3(4H)-Arylamino) Quinazolin-4(3H)-One*; Hindawi Publishing Corporation Scientifica: Cairo, Egypt, 2016; Volume 124, p. 5.
36. Kobra, N.F.; Molaei, F. A concise study on dimedone: A versatile molecule in multicomponent reactions, an outlook to the green reaction media. *J. Saudi Chem. Soc.* **2018**, *22*, 715–741.
37. Wang, G.W.; Lu, Q.Q.; Xia, J.J. Synthesis of N-substituted Acridinediones and Polyhydroquinoline derivatives in refluxing water. *Eur. J. Org. Chem.* **2011**, 4429–4438. [CrossRef]