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Multicomponent Synthesis and Invitro Studies of Tetrahydro Quinazolines-(1H, 3H)-2,5-diones Derivatives Promoted by $ZrOCl_28H_2O$

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***Abstract*-- We have in the present study, an efficient andcost-effective method for the synthesis of derivatives of 7,7-dimethyl-4-phenyl tetrahydroquinazaloine-(1H,3H)-2,5-diones from dimedone, urea and substituted aromatic aldehydes promoted by $ZrOCl_28H_2O$ as a catalyst under ethanol as solvent. The chemical structures of the titled derivatives were determined by ^{1}HNMR &^{13}CNMR, Mass spectral and Elemental analysis. Antimicrobial activities of the titled compounds were also examined by vaious strains and exhibited mild to moderate anti-bacterial and anti-fungal activities.**

***Keywords*-- Dimedone, substituted aromatic aldehydes, 7,7 -dimethyl-4-phenyl Tetrahydro quinazolines-(1H,3H)- 2,5-dione , $ZrOCl_28H_2O$, Antimicrobial activity**

I. Introduction

Multicomponent reactions (MCRs) [1–6] are essential in modern organic and applied chemistry because they enable the precise extraction of target molecules from three or more distinct substrates. They provide a number of advantages over linear-stepwise syntheses and lessen waste production. To stop the creation of dangerous compounds and byproducts from chemical reactions, chemists must create eco-friendly techniques. Because of its special and advantageous qualities—such as enhanced selectivity, reduced energy consumption, superior acoustic cavitation, better raw material consumption, high product yields, and quicker reaction times Due to their biological significance and a number of recent pharmacological activities, tetrahydroquinazolones and their derivatives have drawn a lot of attention. The Biginelli reaction, an acid-catalyzed cyclocondensation reaction of an aldehyde, ethylacetoacetate andurea, was described by Italian chemist Pietro Biginelli in 1893 [1].Many of these bioactive heterocycles also have analgesic and anti-inflammatory properties. Due to their biological significance and a number of recent pharmacological activities, tetrahydroquinazaloine and their derivatives have drawn a lot of attention. The Biginelli reaction, an acid-catalyzed cyclocondensation reaction of an aldehyde, ethyl acetoacetate and urea, was described by Italian chemist Pietro Biginelli in 1893 [1].

Many of these bioactive heterocycles also have analgesic and anti-inflammatory properties. These are due to their biological characteristics, which include potential antibacterial activity against Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus [2], as well as calcium antagonist activity [3]. Octahydroquinazolinones have recently been synthesized using the Biginelli reaction, which substitutes cyclic b-diketones for open chain dicarbonyl compounds [4].The synthesis of Octahydroquinazolinones derivatives using trimethylsilyl chloride (TMSCl) [5], VOSO4 [6], conc. H2SO4, conc. HCl, and ionic is revealed by a review of the literature. Additionally, the corresponding thiazolodine moiety has antifungal and antibacterial properties [7]. As catalysts, silica sulfuric acid [8] Octahydroquinazolinones have recently been synthesized using the Biginelli reaction [9], which substitutes cyclic b-diketones for open chain dicarbonyl compounds. As a result, a number of processes have one or more drawbacks, such as long reaction times, harsh conditions, poor yields from side product formation, and the use of different volatile organic solvents. Therefore, it is still desirable to improve a clean, productive, and environmentally friendly approach. the creation of novel synthetic techniques for the effective synthesis of heterocycles containing 7, 7-dimethyl-4-phenyl Tetrahydro quinazaloine-(1H, 3H)-2,5-dione.intriguing difficulties. Here, we describe a quick pilot reaction between a mixture of dimedone, urea, and substituted aromatic aldehydes that was accelerated by $ZrOCl_28H_2O$ acting as a catalyst in ethanol. .

II. Material And Methods

2.1. Experimental:

Sigma Aldrich provided all of the chemicals, reagents, and solvents. The open capillary method was used to determine the uncorrected melting points of the compounds listed. Ethyl acetate and n-hexane were used in thin layer chromatography (TLC) on a silica gel plate to assess the purity of the newly synthesized compounds. UV light was used in an iodine chamber to visualize the synthesized compounds.

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These compounds' ^{1}HNMR and ^{13}CNMR spectra were captured in $CDCl_3$ solution using BRUKER (400 MHz & 100 MHz) spectrometers. TMS is used as an internal standard to report chemical shifts in parts per million.The Perkin Elmer elemental analyzer was used to perform elemental analyses.

2.2. General procedure for the synthesis of 7, 7-dimethyl-4-phenyl Tetrahydro quinazaloine-(1H, 3H)- 2,5-dione:

Dimedone (1) (10 mmol), aromatic aldehydes (2) (10 mmol), and urea (3) (15 mmol) were combined with an $ZrOCl_2 8H_2O$ (5 mmol) and ethanol as a solvent in a 50 mL beaker. TLC (ethyl acetate/hexane (5:5)) was used to verify the reaction's completion. After that, ethyl acetate was used to extract the reaction mixture, and the catalyst was filtered out. After that, the organic layer cleaned the anhydrous base. The pure corresponding titled compounds (4a–4g) were obtained in good yields by evaporating the organic solvent under low pressure and crystallizing the solid compound from absolute ethanol.

Characterizations:

2.2.1. 4-phenyl)-7,7-dimethyl-,4,6,7,8-Tetrahydro-1H,3H-quinazoline2,5-dione (4a):

Pale yellow solid ; Mp-212-214^{0}C, Yeild-80%, 1HNMR($CHCl_3$) δ ppm: 1.095(s,3H,CH_3), 1.254(s,3H,CH3), 2.159(s,2H,CH_2), 2.243(s,2H,CH_2), 5.512 (s,1H,CH), 7.287-7.541 (m,5H,Ar), 8.179 (s,1H,NH), 9.466 (s,1H,NH);.^{13}CNMR($CHCl_3$)δppm: 195.48, 154.44, 151.25, 148.77, 139.09, 128.53, 125.28, 109.82, 52.58, 49.28, 31.74, 27.54, 25.559;p .Molecular formulae: $C_{16}H_{18}N_2O_2$: Calculated: C-71.08; H- 6.72;N- 10.35. Found: C- 71.02; H- 6.70; N- 10.41.

2.2.2. 7,7-dimethyl 4-(4-hydroxyphenyl)- ,4,6,7,8-Tetrahydro-1H,3H-quinazoline-2,5-dione (4b):

Paleyellowsolid; Mp-212-214^{0}C,Yeild-92%,^{1}HNMR 400MHz,$CDCl_3$)δppm: 0.974(s,3H,CH_3); 1.074(s,3H,CH_3) , 2.118(s, 2H, CH_2), 2.236(s, 2H, CH_2) , 5.322 (s,1H,CH), 7.068-7.415(m, 4H, Ar); 8.712(s, 1H, NH), 9.541 (s,1H,-OH), 10.236 (s, 1H, NH) ; ^{13}CNMR (100MHz, $CDCl_3$) δppm: 194.58, 157.72, 153.07, 151.53, 136.56, 128.44, 118.92, 108.99,52.47, 48.19, 32.87, 27.59, 26.84. LCMS (m/z)-: 287.69 (M+H); Molecularformule: C_{16} H_{18} N_2 O_3; Elemental analysis: calculated: C- 67.12; H-6.34, N- 9.78; Found: C- 67.05, H- 6.33; N- 9.82

2.2.3. 7,7-dimethyl-4-(3,4,5-trimethoxyphenyl)-,4,6,7,8-Tetrahydro-1H,3H-quinazoline-5-dione (4c):

Colorless solid ; Mp-202-204^{0}C,Yeild-94; ^{1}H NMR (400MHz,$CDCl_3$)δ ppm: 1.012 (s, 3H, CH_3); 1.16(s,3H,CH_3), 2.254(s, 2H, CH_2), 2.445(s,2H,CH_2), 3.781(s, 3H, (OCH3), 3.578 (s, 6H, (OCH3)2), 5.259 (s,1H,CH), 7.180-7.254(m, 2H, Ar); 8.725(s, 1H, NH); 9.839(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$) δppm : 194.62, 165.45, 152.58, 138.98 , 135.46, 128.20, 123.52, 109.07 , 105.53 , 59.45 , 52.66, 50.48, 33.52 , 28.07, 27.43; LCMS (m/z) 360.71. Molecularformule: C_{19} H_{24} N_2 O5: Elemental analysis: calculated C- 63.32; H- 6.71, N-7.77; Found: C- 63.30, H- 6.70; N- 7.82

2.2.4. 7,7-Dimethyl-4(4-Ethylphenyl)-,4,6,7,8-Tetrahydro-1H,3H-quinazoline-2,5-dione (4d).

Colorless solid; mp-228- 230^{0}C: Yeild-87%, ^{1}H NMR (400MHz,$CDCl_3$) δppm: 0.914(s, 3H, CH_3); 1.088(s, 3H, CH_3); 2.115 (s, 2H, CH_2); 2.236 (s,2H, CH_2), 2.430(s, 3H, CH_3), 5.257 (s,1H,CH), 7.048-7.445 (m, 4H, Ar); 9.263(s, 1H, NH); 10.026 (s, 1H, NH);^{13}CNMR(100MHz, $CDCl_3$)δppm: 195.28 , 152.47, 151.08, 147.73, 135.45, 128.05, 126.72, 108.55, 56.47,49.47, 32.45, 28.56, 26.46, 20.75 19.02.LCMS (m/z)-249.58 (M+H). Molecularformule: C_{14} H_{22} N_2 O2: Elemental analysis: calculated; C- 67.90; H- 6.68, N- 9.30; Found: C- 67.89, H- 6.67; N- 9.35.

2.2.5. 4-(4-Chlorophenyl)-7,7-dimethyl-,4,6,7,8-Tetrahydro -1H,3H-quinazoline2,5-dione (4e):

Pale pink solid; mp-235-237^{0}C , Yeild-87%, ^{1}HNMR(400MHz,$CDCl_3$)δppm: 0.975(s,3H, CH_3); 1.15(s, 3H, CH_3); 2.156 (s, 2H, CH_2); 2.409 (s, 2H, CH2); 5.554 (s,1H,CH), 7.119-7.434 (m, 4H, Ar); 9.786(s, 1H, NH); 10.345(s, 1H, NH); 13C NMR ((100MHz,$CDCl_3$)δppm: 195.15, 173.48 , 147.79 , 140.45, 131.37, 131.81,130.45, 128.73, 127.41, , 106.76, 51.52, 49.44 , 32.50, 28.75, 26.56; LCMS (m/z) 305.54(M+H).Molecularformule: C_{16} H_{17} Cl N_2 O2; Elemental analysis: calculated C- 63.05; H- 5.62, N- 8.19; Found: C- 63.03, H- 5.60; N- 8.23

2.2.6. 4-(4-Bromophenyl)-7,7-dimethyl-,4,6,7,8-Tetrahydro -1H,3H-quinazoline2,5-dione (4f):

Pale red solid; mp - 232-236^{0}C; Yeild-86%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.978(s, 3H, CH_3); 1.13(s, 3H, CH_3), 2.155(s, 2H, CH_2); 2.436(s, 2H, CH_2); 5.512 (s,1H,CH), 7.312 (d, J=8.5Hz, 2H, Ar), 7.530 (d, J=8.4Hz, 2H, Ar), 9.566(s, 1H, NH); 10.337(s, 1H, NH); ^{13}C NMR (100MHz, ,$CDCl_3$) δppm:194.55, 173.59 , 149.59 , 141.25, 130.54, 129.62, 128.31, 122.46, 108.76, 50.26, 47.55 , 32.19, 28.58, 26.42 ;LCMS (m/z) 350.45.(m+H).

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Molecularformule C17 H_{17} Br N_2 O2: Elemental analysis: calculated: C- 55.03; H- 4.91, N- 8.02; Found: C- 55.01, H- 4.89; N- 8.05.

2.2.7. 7, 7-dimethyl -4-(4-nitrophenyl)-, 4, 6, 7, 8-Tetrhydro-1H,3H-quinazoline-2,5- dione (4g):

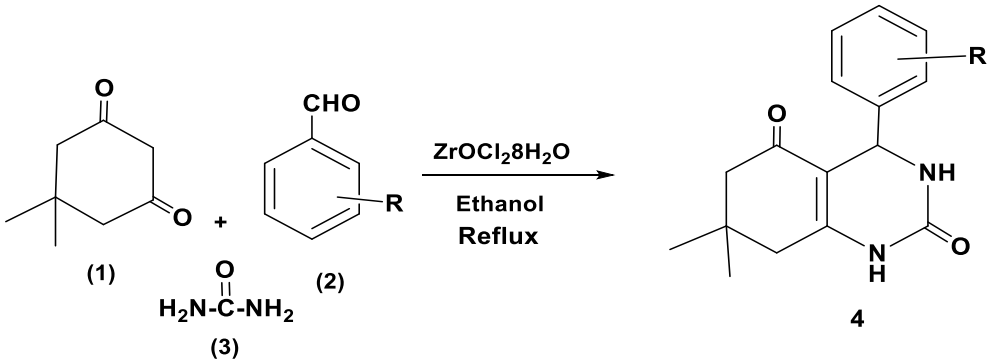
Yellow solid; mp:.237-237,Yeild-85%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.954(s,3H, CH_3); 1.058(s, 3H, CH_3); 2.21(s, 2H, CH_2); 2.41(s,2H, CH_2); 5.745 (s,1H,CH), 7.437-7.884 (m, 4H, Ar);9.152(s, 1H, NH); 9.899(s, 1H, NH); ^{13}C NMR (100MHz,$CDCl_3$):δppm:L195.14,153.28,151.56,148.59,14 5.39,128.45,124.54,105.18,50.48,48.47,32.28,28.21, 26.46, LCMS(m/z)-316.35(M+H); Molecularformule: $C_{16}H_{17}N_3O_4$; Elemental analysis: calculated: C-60.94;H- 5.43, N- 13.33; Found: C- 60.92, H- 5.42; N- 13.38.

III. Results And Discussion

3.1. Chemistry:

Initially, the titled analogous can be prepared and simple, effective, and economical method process.

The reaction of substituted aromaticldehydes, dimedone, and urea in the presence of $ZrOCl_28H_2O$ under solvent conditions at reflux was initially found to yield the best results (Scheme -1).There are no dangerous organic solvents used in the current process. This catalyst has promising features for the reaction response such as the shortest reaction time, excellent product yields, and simple work-up. It has been noted that different substituted aromatic aldehydes with electron-releasing or withdrawing substituents in para-positions result in a high product yield. In this instance, we found that aromatic aldehydes with electron-withdrawing groups reacted more quickly than aldehydes with electron-donating groups. Aromatic aldehydes and thiourea were found to react well. Compared to the moiety's EDG, the microbial activity of titled moiety with EWG showed more active potential (Scheme-1)



(4a-4g)

R = H, 4-OH,3,4,5$(OCH_3)_3$,4-C_2H_5,4-Cl,4-Br,4-CN,4-NO_2

Scheme-1

This reaction was studied under optimization by different catalysts, various amounts of the catalyst. The different amounts of catalyst were added during the reaction, the major adduct of the analogous were synthesized in the presence of natural protic acid and natural lemons whereas other Bronsted acids such choline chloride acid as shown in (Table-1).

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Table-1:
The effect of catalyst for preparation of titled derivatives (4c):

Entry	Catalyst	Temperature (^{0}C)	Time (hrs.)	Yield (%)
1	$FeCl_3$	75	5	58
2	$AlCl_3$	75	5	62
3	$ZrOCl_2 8H_2O$	75	5	94
4	TiO_2	75	5	71

The structures of the desired analogous were constructed on the basis of advanced spectroscopic data by ^{1}HNMR, ^{13}C NMR, molecular weight spectral and elemental analyses. The proton NMR evidences of corresponds to derivatives that appears at various protons O-H, N-H, aromatic C-H above values represented in characterization of derivatives **(4a-4g).**

3.2. Antibacterial Activity:

The substituted 7,7-dimethyl-4-phenyl-Tetrahydroquinazaloine-(1H,3H)-2,5-diones (4a-4g) and its derivatives have been investigated in vitro for their potent antibacterial activity against bacterial strains like *S. aureus, E. coli, S. typhi, and B. substills*, as well as fungi like *A. Niger* and *C. albicans*. Agar plates with Sabouraud dextrose broth for fungi and nutrient broth for bacteria were used to examine the test compound's in vitro activities. Every microbial species was tested against the test compound. The test compound's antibacterial potencies have been compared to those of fluconazole (fungi) and streptomycin (bacteria).Table-2 summarizes the test compound's antimicrobial inhibitions, which are expressed as the area of zone of inhibition. The Quinazalones ring system and this family of compounds' high hydrophobic content may be the cause of their notable antibacterial activity. Quinazalones-containing compounds have greater antibacterial activity. This prevents their diffusion in the agar medium, presumably as a result of the latter's strong interaction with the medium.

Table-2:
Antimicrobial activity of synthesized derivatives (4a-4g):

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. Niger	C. albicans
4a	07	08	08	06	07	09
4b	20	21	19	18	16	15
4c	21	19	18	18	17	16
4d	13	12	10	13	10	11
4e	20	21	20	18	17	14
4f	21	19	19	18	14	15
4g	07	10	08	06	16	17
streptomycin	25	25	22	22	NA	NA
flucnozole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

Invitro antibacterial activity of the desired compounds (4a–4g) was recognized to be low for the electron attracting group (4e, 4f, and 4g) and moderate for the electron donating group (4b, 4c, and 4d).

The compound “4e and 4f” were showed excellent active potent due to halogen group present in the compound. Additionally, we noticed that the antifungal activity of compounds (4a–4g) varied. The compound "4b, 4c and 4d" demonstrated good activity, while the rate of the compound” 4a and 4g” showed low to moderate activity.

IV. CONCLUSION

In conclusion, an effective catalyst for this synthesis of a number of substituted compounds. The current methodology has many appealing features, including quick reaction times, high yields, and simple product isolation. This method is both economically and environmentally benign due to its simplicity, $ZrOCl_28H_2O$ used as a catalyst and ethanol as solvent conditions, and eases of catalyst recovery and reuse. For the synthesis of the desired derivaties (4a-4g) and its derivatives of biological and medicinal significance, we think this process is practical, affordable, and environmentally friendly.

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