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ONE POT SYNTHESIS OF SERIES OF 7, 7-DIMETHYL-4-PHENYL -TETRAHYDRO QUINAZALONES-(1H, 3H) - 2, 5-DIONES EMPLOYING BRONSTD ACID AND BIOEVLUATION

Seera Durga Prasad[1] and Dr. N. Krishnarao[1]*

[1]*Department of Organic Chemistry, PRISM PG & DG College (Affiliated to Andhra University), Visakhapatnam, India, 530016.

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***Corresponding Author**
N. Krishnarao
Department of Organic Chemistry, PRISM PG & DG College (Affiliated to Andhra University), Visakhapatnam, India, 530016.

ABSTRACT
The present investigation, an efficient and cost-effective method for the synthesis of derivatives of 7,7-dimethyl-4-phenyl tetrahydroquinazaloine- (1H,3H)-2,5-diones promoted by Methanesulphonic acid dimedone, urea and substituted aromatic aldehydes employing camphorsulfonic acid as acatalyst under solvent free condition. The chemical structures of the titled compounds were confirmed by 1H-NMR & 13CNMR, 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 acid aldehydes, 7,7 -dimethyl-4-phenyl Tetrahydro quinazalones-(1H,3H)- 2,5-dione, Methanesulfonicacid, Bioevluation.

1. INTRODUCTION
Tetrahydroquinazaloine and its analogous, have received more and considerable attention because of biological significant and number of pharmacological activities in now a days. In 1893, Italianchemist Pietro Biginelli reported on the acid catalyzed cyclocondensationreaction of an aldehyde, ethylacetoacetate andurea, a procedure known as Biginelli reaction.[1] A number of these bioactive heterocycles also function as analgesic and Anti-inflammatory agents. These are owing to their biological properties such as potential antibacterialactivity against Pseudomonas aeruginosa Escherichia coli, Staphylococcus aureus.[2] and also as a calciumantagonist activity.[3] More recently, the Biginelli reaction has been employedfor the synthesis of octahydroquinazolinones, which used cyclicb-diketones instead of open chain dicarbonyl compounds.[4] Literature survey reveals that the synthesisof octahydroquinazolinone derivatives using Trimethylsilylchloride (TMSCl)[5], $VOSO_4$[6], conc. H_2SO_4, conc. HCl, ionic. The correspondingthiazolodine moiety also possesses antibacterialand antifungal activities.[7] Silicasulfuric acid[8] as catalysts. More recently, the Biginelli reaction has been employedfor the synthesis of octahydroquinazolinones[9], which used cyclicb-diketones instead of open chain dicarbonyl compounds. Hence, several procedures suffer from one or more disadvantages viz; prolonged time period harsh reaction conditions, prolonged time peri, pooryields due formation of side products and use of various volatile organic solvents. So, the improvement of a clean, good yielding and eco-friendly approach is still desirable.

Initially, a pilot reaction was attempted using substituted aryl aldehyde (1), dime done (2) and thiourea (3) in the presence of Methanesulphonic acid as Lews catalyst (Scheme-I).

2. MATERIAL AND METHODS
All the chemical, reagents and solvents were commercially purchased from Sigma Aldrich**.** The melting points of the titled compounds were determined by open capillary methode and are uncorrected. The purity of thenewly synthesized compounds was checked by thin layer chromatography (TLC) on silica gel plate using ethylacetate and n-hexane. Synthesized compounds were visualized with UV light in iodine chamber. 1HNMR & ^{13}CNMR spectra of these compoundes were recorded on BRUKER (400 MHz & 100 MHz) spectrometers in $CDCl_3$ solution. Chemical shifts are reported in ppm using TMS as an internal standard. Elemental analyses were carried out in Perkin Elmer elemental analyzer.

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

A mixture of dimedone (1) (1mol), aromatic aldehydes (2) (1mol), and urea (3) (1.5 mol) with the methanesulfonicacid acid (2.0mol) without solvent taken in a 100 mL beaker. The completion of the reaction was checked by TLC (ethyl acetate/hexane (4:6). The reaction mixture was then extracted with ethyl acetate and the catalyst was separated by the filtration. The organic layer then washed anhydrous base. Organic solvent was evaporated under reduced pressure and solid compound was crystallized from absolute ethanol to lead the pure corresponding titled compounds **(4a–4g)** in good yields.

Charecterization

2.1.1. 4-phenyl)-7, 7-dimethyl-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline2, 5-dione (4a)

Yellow solid; Mp: 224-226^{0}C, **Yeild**-87%, **1HNMR(CHCl$_3$)ppm:** 0.957(s,3H,CH_3), 1.012 (s,3H, CH_3), 2.019(d, J=8.4Hz,2H,CH_2), 2.543(d, J=7.5Hz,2H,CH_2), 5.021(d,J=2.4Hz, 1H,CH), 7.254-7.441(m,5H,Ar), 7.994(s,1H,NH),9.046 (s,1H,NH).**^{13}CNMR(CHCl$_3$)δppm:** 192.58, 152.84, 150.25,149.77,138.09, 128.73, 124.58,107.42,51.78, 48.88,32.74, 28.74,26.89. Molecular formula: $C_{16}H_{18}N_2O_2$: Calculated: C-71.09; H, 6.71;N, 10.36. Found: C, 71.06; H, 6.70; N, 10.39.

2.1.2.4-(4-Chlorophenyl)-7,7-dimethyl-,4,6,7,8-Tetrahydro-1H,3H-quinazoline2,5-dione (4b)

Yellow solid; Mp: 214-216^{0}C,Yeild-83%, ^{1}H NMR (400MHz,$CDCl_3$)δppm: 0.995(s, 3H, CH_3); 1.115(s, 3H, CH_3); 2.215 (d, J=8.0Hz, 2H, CH_2); 2.440(s, 2H, CH_2); 5.226 (d, J=12.4Hz, 1H, CH); 7.129-7.344 (m, 4H, Ar); 9.786(s, 1H, NH); 10.145(s, 1H, NH); ^{13}C NMR (100MHz,$CDCl_3$)δppm:195.55, 173.58, 147.09, 140.85, 131.57, 131.71,130.25, 128.33, 127.01, 108.06, 51.82, 49.44, 32.40, 28.75, 26.76; 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

2.1.3.4-(4-Bromophenyl)-7,7-dimethyl-,4,6,7,8-Tetrahydro-1H,3H-quinazoline2,5-dione (4c)

Yellow solid **Mp** -254-256^{0}C; **Yeild-8**8%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.948(s, 3H, CH_3); 1.103(s, 3H, CH_3); 2.015(d, J=8.8Hz, 2H, CH_2); 2.338(s, 2H, CH_2), 5.124(d, J=8.0Hz, 1H, CH); 7.142 (d, J=8.8Hz, 2H, Ar); 7.330(s, J=5.8Hz, 2H, Ar); 9.686(s, 1H, NH); 10.037(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm: 194.45, 170.59, 145.89, 141.55, 130.74, 129.52, 128.01, 122.56, 108.76, 50.76, 47.55, 32.79, 28.48, 26.72; LCMS(m/z):350.74.(M+H). Molecularformule C_{17} H_{17} Br N_2 O_2: Elemental analysis: calculated: C- 55.03; H- 4.91, N- 8.02**;** Found: C- 55.01, H- 4.89; N- 8.05.

2.1.4.7,7-dimethyl-4-(3,4,5-trimethoxyphenyl)-, 4,6,7,8-Tetrahydro-1H,3H-quinazoline-5-dione (4d)

Yellow solid Mp- 204-206^{0}C; Yeild-94%, ^{1}H NMR (400MHz,$CDCl_3$)δ ppm: 1.048(s, 3H, CH_3), 1.116(s, 3H, CH_3); 2.218(d, J=9.4Hz, 2H, CH_2); 2.545(d,J=10.4Hz,2H,CH_2); 3.781(s, 9H, 3(OCH_3)), 5.219(d, J=8.8Hz, 1H, CH), 6.980(s,2H, Ar-H); 8.825(s, 1H, NH), 9.359(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$) δppm: 195.32, 164.55, 153.78, 138.18, 136.76, 128.20, 122.02, 109.27, 104.73, 59.55, 52.76, 50.88, 33.72, 28.47, 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.

2.1..5 7,7-dimethyl 4-(4-hydroxyphenyl)-, 4,6,7,8-Tetrahydro-1H,3H-quinazoline-2,5-dione (4e)

Yellow solid; Mp: 254-256^{0}C;. Yeild-90%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.966(s,3H, CH_3); 1.110(s,3H,CH_3); 2.118(d,J =10.2Hz, 2H, CH_2); 2.240(d,J=12.6Hz, 2H, CH_2); 5.116(d, J=6.8Hz, 1H, CH); 6.885-7.224(m, 4H, Ar); 8.912(s, 1H, NH);10.024(s,1H,-OH), 10.236(s, 1H, NH); ^{13}CNMR (100MHz,$CDCl_3$)δppm:192.58,156.42,152.77,150.83,134.76, 128.54, 117.72, 106.59,51.77,48.59,32.04,27.09,26.14; LCMS (m/z)-287.58(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- 67.10, H- 6.33; N- 9.82.

2.1.6.7,7-Dimethyl-4(4-Ethylphenyl)-,4,6,7,8-Tetrahydro-1H,3H-quinazoline-2,5-dione (4f).

Yellow solid; Mp- 251- 253^{0}C: **Yield**-89%, ^{1}H NMR (400MHz,$CDCl_3$) δppm: 0.895(s, 3H, CH_3); 1.112(s, 3H, CH_3); 2.111(d, J=8.4Hz, 2H, CH_2), 2.158(d,J-9.6Hz, 2H, CH_2); 2.330(s, 3H, CH_3),5.025(s,1H,CH),7.280-7.645(m,4H,Ar),9.654(s,1H,NH);10.026(s,1H,NH); ^{13}CNMR (100 MHz, $CDCl_3$): δppm: 194.78, 150.97, 150.08, 148.53, 134.85, 128.55, 125.52, 106.75, 56.07, 49.77, 32.45, 28.76, 26.46, 20.45 19.52.LCMS (m/z)-249(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.

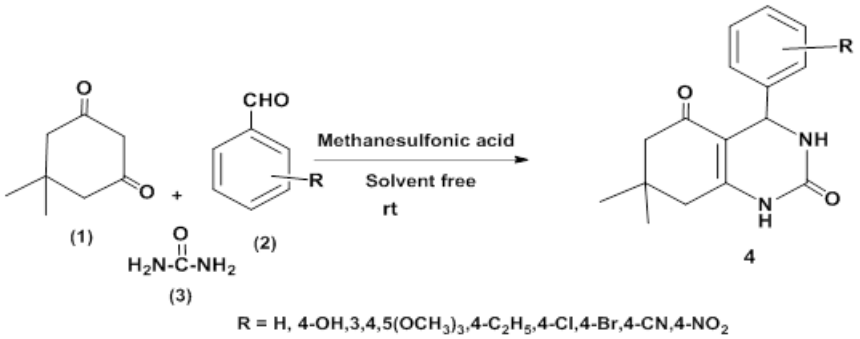
2.1.7 7, 7-dimethyl -4-(4-nitrophenyl)-, 4, 6, 7, 8-Tetrhydro-1H,3H-quinazoline-2,5- dione (4g)

Yellow solid; p-245-247^{0}C,Yeild-85%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.894(s,3H,CH_3); 1.118(s, 3H, CH_3); 2.121(d, J=7.6Hz, 2H, CH_2); 2.227(d,J=8.0Hz,2H, CH_2); 5.217(d, J=8.0Hz, 1H, CH); 7.354-7.844 (m, 4H, Ar);9.212(s, 1H, NH); 9.789(s, 1H, NH); ^{13}C NMR(100MHz,$CDCl_3$)δppm:196.12,154.08,151.62,149.09, 145.39,128.55,124.14,105.28,50.48, 48.27,32.68,28.51, 26.86, LCMS (m/z)-316.28(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.

3. RESULTS AND DISCUSSION

Initially, we found that the best result investigated the reaction of substituted aromatic aldehyde, dimedone and

urea in the presence of methanesulphonicacid under solvent free conditions at room temperture **(Scheme -1).** The present process does not involve any hazardous organic solvents. This catalyst has most advantages features for the reaction response such as the shortest reaction time, excellent product yields, and simple work-up. It is reveals that the various substituted aromatic aldehydes possess electron-releasing or withdrawing substituents in para-positions lead good yield of the product. Here, we have observed that the reaction of aromatic aldehydes bearing electron-withdrawing groups was rapid as compared to the reaction of aldehydes having electron donating groups. It was identified that the reaction of aromatic aldehydes with thiourea got excellent. The microbial activity of titled moeity possesses EWG exhibited more active potento than the EDG of the moeity **(Scheeme-1).**



Scheeme-1

3.1. ANTIBACTERIAL ACTIVITY

The invitro antibacterial activity of the newly titled compounds enhanced viz; The substituted7,7-dimethyl-4-phenyl-Tetrahydroquinazaloine-(1H,3H)-2,5-diones and its derivatives have being examined in vitro for its potent active bacterial strains such as, S.aureus E.coli S. typhi B.substills. and fungi viz; A. niger, C. albicans. The in vitro activities of the test compound were studied using agar plates containing Sabourauds dextrose broth for fungi and in nutrient broth for bacteria. The test compound was tested against each microbial species. The antibacterial potencies of the test compound have being compared with Streptomycin (bacteria) and Ketonozole (fungi). The antimicrobial inhibitions of test compound are expressed as the area of zone of inhibition and summarized in **Table-1**. This marked and antibacterial activity may be due to the presence of high hydrophobic content of this family of compounds and the quinazalones ring system. The compounds containing the quinazalones segment are more active against bacteria. Presumptively due to the strong interaction of the later with the agar medium, this hinders their diffusion in agar medium.

Table I: Antimicrobial assay of activity synthesized scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
4a	07	09	08	07	04	05
4b	18	21	19	20	15	16
4c	21	20	18	19	17	16
4d	12	13	15	11	12	13
4e	15	16	15	12	09	08
4f	12	11	12	10	09	11
4g	05	08	10	12	15	17
streptomycin	25	25	25	25	NA	NA
Ketonozole	NA	NA	NA	NA	22	22
DMSO	---	----	---	---	---	---

4. CONCLUSION

In conclusion, an efficient catalyst for the synthesis of series of desired compounds. The present methodology is very attractive features such as short reaction times, good yields, and easy of product isolation. This is a simple procedure and solvent free conditions combined with easy recovery and reuse of Methanesulphonic acid catalyst make this method economically and environmentally benign process. We believe that this procedure is convenient, economic and ecofriendly for the synthesis of the substituted 7,7-dimethyl-4-phenyl Tetrahydro quinazaloine-(1H,3H)- 2,5-diones and its derivatives of biological as well as medicinal importance.

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