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SOLVENT FREE BIO ACTIVE SYNTHESIS OF SUBSTITUTED 7, 7-DIMETHYL-4-PHENYL -TETRA HYDRO QUINAZALOINE-(1H, 3H) - 2, 5-DIONES EMPLOYING METHANE SULFONIC ACID

P. Kishore Kumar, K. Bhaskara Rao, M. Divya and Dr. N. Krishnarao*

PRISM PG & DG College (Affiliated by Andhra University), Visakhapatnam, India.

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***Corresponding Author**
Dr. N. Krishnarao
PRISM PG & DG College (Affiliated by Andhra University), Visakhapatnam, India.

ABSTRACT

We have in the present in depth study, an efficient and cost-effective process for the synthesis of derivatives of 7,7-dimethyl-4-phenyl tetrahydroquinazaloine- (1H,3H)-2,5-diones using dimedone, urea and substituted aromatic l aldehydes employing methanesulphonic acid as catalyst as well as solvent free condition. The structures of the desired compounds were analyzed by ^{1}H-NMR & ^{13}CNMR, Mass spectral as well as elemental analysis. The activities of an antimicrobial study of the titled compounds were also examined by vaious strains and exhibited mild to moderate anti-bacterial and anti-fungal activities.

KEYWORDS: Dimedone, substituted arylaldehydes, 7,7 -dimethyl-4-phenyl Tetrahydro quinazaloine-(1H,3H)- 2,5-dione**,** Methanesulfonicacid, Antimicrobial.

1. INTRODUCTION

Quinazaloine and its derivatives, have received considerable attention due to biological importance and numerous pharmacological properties in recent years. The acid catalyzed cyclocondensation reaction of an aldehyde, ethyl acetoacetate and urea, a procedure reported by as Biginelli reaction.[1] The various bioactive heterocycles having characteristics function as analgesic, anti-inflammatory agents, antibacterial.[2], calcium antagonist 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[6], conc. H_2SO_4, conc. HCl, ionic. Silicasulfuric acid[8] as catalysts. More recently, the Biginelli reaction has been employedfor the synthesis of octahydroquinazolinone.[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.

2. MATERIAL AND METHODS

All the reagents, chemical and solvents were procured from Merck. The melting points of the desired compounds were determined by open capillary methode and are uncorrected. The purity of the newly prepared compounds was monitored by thin layer chromatography (TLC) on silica gel plate using ethylacetate and n-hexane. The synthesized compounds were visualized with UV light in iodine chamber. 1HNMR &^{13}CNMR spectra of these compounds were measured 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.

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

A mixture of dimedone (1) (1mol), aryl aldehydes (2) (1mol), and urea (3) (15 mmol) with the methane sulfonic acid (10 mol) without solvent taken in a 50mL four neck RBF. The completion of the reaction was monitored by TLC (ethyl acetate/hexane (5:5). The reaction mixture was extracted with ethyl acetate and the catalyst was separated by the filtration. The organic layer then washed a solution of sodium bi carbonate and washed with water in twice and also separated by organic layer. 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

4.1. 4-phenyl)-7, 7-dimethyl-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline2, 5-dione (4a)

Pale brown solid; m.p: 254-256^{0}C, **Yeild**-85%, **1HNMR($CHCl_3$)ppm:** 0.955(s, 3H, CH3), 1.112(s, 3H, CH_3), 2.139(q, J= 8.8Hz, 2H, CH2), 2.443(q, J= 9.0.2Hz, 2H, CH2), 5.526(d, J= 7.6Hz, 1H, -CH-), 7.274-7.421(m,

5H, Ar-H), 7.987(s, 1H, NH), 9.246 (s, 1H, NH).**^{13}CNMR(100MHz, $CHCl_3$)ppm:** 190.28, 151.64, 149.55, 148.67, 137.89, 128.63, 125.88, 108.92, 52.58, 48.18, 31.48, 28.44, 27.09. **Molecular formulae**: $C_{16}H_{18}N_2O_2$:clculated: C-71.09; H, 6.71;N, 10.36. Found: C, 70.95; H, 6.70; N, 10.42.

2).4-(4-Chlorophenyl)-7, 7-dimethyl-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline2, 5-dione (4b)
White solid, m.p: 241-242^{0}C, **Yeild**-88%, ^{1}H NMR (400MHz, $CDCl_3$)δppm: 0.905(s, 3H, CH_3); 1.165 (s, 3H, CH3); 2.125 (q, J= 9.0Hz, 2H, -CH_2); 2.340 (s, 2H, -CH_2); 5.126 (d, J= 7.6Hz, 1H, -CH-); 7.344-7.519 (m, 4H, Ar-H); 9.586(s, 1H, NH); 10.245(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$)δppm: 193.55, 172.28, 146.99, 141.05, 132.78, 131.01, 130.35, 128.63, 127.18, 107.76, 51.92, 48.54, 32.45, 28.15, 27.46; LCMS (m/z): 306.22(M+2). **Molecularformule:** C_{16} H_{17} Cl N_2 O_2; **Elemental analysis: calculated** C- 63.06; H- 5.62, N- 8.20**; Found**: C- 63.00, H- 5.61; N- 8.26.

3).4-(4-Bromophenyl)-7, 7-dimethyl-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline2, 5-dione (4c)
Pale red solid, m.p-254-256^{0}C; **Yeild**-88%, ^{1}HNMR (400MHz, $CDCl_3$)δppm: 0.898(s, 3H, CH_3); 1.103(s, 3H, CH_3); 2.015(q, J=10.4Hz, 2H, CH_2); 2.312(s, 2H, -CH_2); 5.102(d, J=8.0Hz, 1H, -CH-); 7.112 (d, J=8.4Hz, 2H, Ar-H); 7.324(d, J=8.0Hz, 2H, Ar-H); 9.245(s, 1H, NH); 10.158(s, 1H, NH); ^{13}C NMR (100MHz, , $CDCl_3$) δppm: 193.55, 174.49, 150.46, 140.85, 130.66 129.58, 128.58, 122.33, 107.86, 51.27, 48.53, 32.59, 28.08, 26.82 ;LCMS (m/z) 351.14.(m+2). **Molecularformule** C_{17} H_{17} Br N_2 O_2: **Elemental analysis: calculated:** C- 55.04; H- 4.92, N- 8.06**; Found**: C- 54.97, H- 4.91; N- 8.12.

4)7, 7-dimethyl-4-(3, 4, 5-trimethoxyphenyl)-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline-5-dione (4d)
White solid, m.p- 189-191^{0}C; **Yeild**-90%, ^{1}H NMR (400MHz, $CDCl_3$)δ ppm: 1.208(s, 3H, CH_3); 1.316(s, 3H, CH_3); 2.126(q, J= 9.4.4Hz, 2H, CH_2); 2.455(q, J= 12.6Hz, 2H, -CH_2); 3.687(s, 9H, 3(OCH_3)), 5.109(d, J= 6.8Hz, 1H, CH); 6.745(s, 2H, Ar-H); 8.749(s, 1H, NH); 9.437(s, 1H, NH); 13C NMR (100MHz, $CDCl_3$)δppm: 192.32, 165.65, 152.88, 139.82, 135.66, 128.87, 122.55, 110.97, 103.93, 58.75, 52.46, 51.78, 33.62, 28.57, 27.73; **LCMS (m/z) 360.71**. **Molecularformule:** C_{19} H_{24} N_2 O_5: **Elemental analysis: calculated** C- 63.32; H- 6.71, N- 7.77; **Found:** C- 63.30, H- 6.70; N- 7.82.

.**5) 7, 7-dimethyl 4-(4-hydroxyphenyl)-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline-2, 5-dione (4e)**
White solid, m.p:248-249^{0}C;**. Yeild-89**%, **^{1}HNMR (400MHz, $CDCl_3$)δppm**: 0.896(s, 3H, CH_3); 1.017(s, 3H, CH_3); 2.115(q, = 10.8Hz, 2H, CH2); 2.356(q, J=12.4.2Hz, 2H, CH_2); 5.244(d, J=8.4Hz, 1H, -CH); 6.774-7.128(m, 4H, Ar-H); 8.658(s, 1H, NH), 9.264(s, 1H, -OH), 9.566(s, 1H, NH);**^{13}CNMR (100MHz, $CDCl_3$)δppm**: 191.58, 158.72, 151.88, 149.63, 135.76, 128.98 118.42, 106.59, 51.47, 48.44, 31.77, 27.96, 26.84. **LCMS (**m/z)- 287.42(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.

6)7, 7-Dimethyl-4(4-Ethylphenyl)-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline-2, 5-dione (4f).
White solid, m.p: 252-254^{0}C: **Yeild**-90%, **^{1}H NMR (400MHz, $CDCl_3$)δppm**: 0.877(s, 3H, CH3); 1.124(s, 3H, CH3); 2.146(q, J= 9.0Hz, 2H, -CH_2); 2.243(q, J= 10.8Hz, 2H, CH_2); 2.124(s, 3H, CH3), 4.945(s, 1H, CH); 7.048-7.464 (m, 4H, Ar-H); 9.146(s, 1H, NH); 9.847(s, 1H, NH);**^{13}CNMR(100MHz**, **$CDCl_3$) δppm**: 192.28, 151.57, 150.45, 149.46, 134.78, 128.85, 126.82, 106.65, 56.74, 48.47, 31.65, 28.47, 27.86, 21.11, 19.54. **LCMS** (m/z)-249.45(M+H). **Molecular formule**: C_{14} H_{22} N_2 O_2: **Elemental analysis: calculated**; C- 67.90; H- 6.68, N- 9.30; Found: C- 67.89, H-6.67; N- 9.35.

8).7, 7-dimethyl -4-(4-nitrophenyl)-, 4, 6, 7, 8-Tetrhydro-1H, 3H-quinazoline-2, 5- dione (4g): Paleyellowsolid, m.p:.301-303, **Yeild**- 84%, **^{1}HNMR (400MHz, $CDCl_3$)δppm**: 0857(s, 3H, CH3); 1.113(s, 3H, CH3); 2.21(q, J=16.4Hz, 2H, CH_2); 2.41(q, J=16.9Hz, 2H, CH_2); 5.34(d, J=2.4Hz, 1H, CH); 7.37-7.84 (m, 4H, Ar);9.12(s, 1H, NH); 9.89(s, 1H, NH**); ^{13}C NMR (100MHz, $CDCl_3$)δppm:**193.45, 152.28, 150.46, 147.29, 146.89, 128.95, 126.84, 106.98, 51.88, 49.87, 31.88, 28.51, 27.86, **LCMS(**m/z)-316(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.

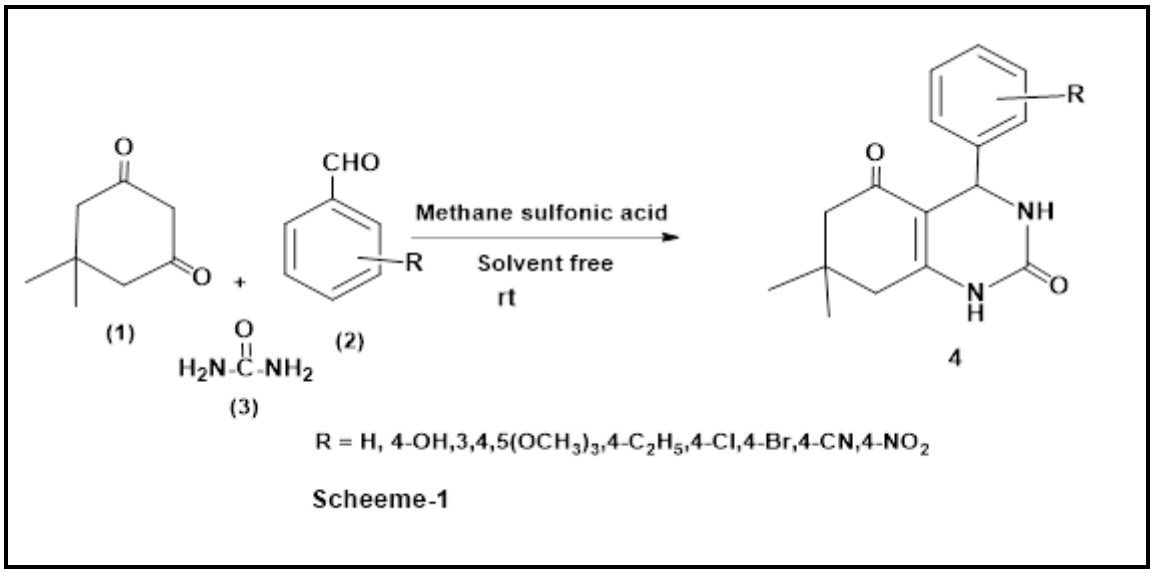
Antibacterial Activity
In vitro antibacterial activity of the newly prepared compounds enhanced viz; The substituted 7, 7-dimethyl-4-phenyl-Tetrahydroquinazaloine-(1H, 3H)-2, 5-diones and its derivatives have being examined in vitro for its potent active bacterial strains such as, **S.aureus E.coli S. typhi B.substills. and fungi viz; A. niger, C. albicans**. The *in vitro* activities of the test compound were evaluated using agar plates containing Sabourauds dextrose broth for fungi and in nutrient broth for bacteria. The newly prepared compound was examined against each microbial species. The antibacterial potencies of the desired compound have being compared with standard drug **Streptomycin** (bacteria) and **Flucozole** (fungi). The antimicrobial inhibitions of test compound are measured 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 quinazalone ring system. The compounds possesses the quinazaloine 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 activity screening 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	08	08	09	06	08	06
4b	21	20	18	19	17	16
4c	21	18	19	20	15	16
4d	12	13	11	14	11	12
4e	11	12	13	08	07	08
4f	10	14	13	11	08	08
4g	07	09	11	12	14	15
streptomycin	25	25	22	22	NA	NA
flucnozole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

5. RESULTS AND DISCUSSION

Initially, we found that the excellent result investigated the reaction of substituted aromatic aldehyde; dimedone and urea in the presence of methane sulfonic acid under solvent free conditions at room temperture **(Scheme -1).** The present method does not use any hazardous organic solvents. The advantages of this catalyst having some important features for the reaction response such as the shortest reaction time, excellent product yields, and simple work-up. It is observed that various substituted aromatic aldehydes containing electron-donating or withdrawing substituents in para-positions lead good yield of the product. Here, we have observed that the reaction of aromatic aldehydes having electron-withdrawing groups was rapid as compared to the reaction of aldehydes having electron donating groups. It was observed that the reaction of aromatic aldehydes with thiourea got good yeild. The microbial activity of titled moeity possesses EWG exhibited more active potento than the EDG of the moeity **(Scheeme-1).**



Scheeme-1

6. CONCLUSION

In conclusion, an efficient catalyst for the synthesis of derivative titled compounds. The present methodology is very attractive features such as short reaction times, good yields, and easay of product isolation. This is a simple procedure and solvent free conditions and 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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