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SOLVENT FREE SYNTHESIS OF SERIES OF 7, 7-DIMETHYL-4-PHENYL - TETRAHYDRO QUINAZALOINE-(1H, 3H)-2, 5-DIONES EMPLOYING METHANESULFONIC ACID AND BIOEVALUATION

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ABSTRACT

The present investigation of efficient and cost-effective method for the synthesis of 7, 7-dimethyl-4-phenyl tetrahydroquinazaloine-(1H, 3H)-2, 5-dionesderivatives employing dimedone, urea and substituted aromatic aldehydes using methane sulfonic acid as a catalyst under solvent free condition. The newly synthesized compounds were analysed by ^{1}H-NMR and ^{13}CNMR, Mass spectral and Elemental analysis. Antimicrobial activities of the titled compounds were also examined by various strains and exhibited mild to moderate anti-bacterial and anti-fungal activities.

KEYWORDS

Dimedone, Substituted aromatic aldehydes, 7, 7 -dimethyl-4-phenyl tetra hydro quinazaloine-(1H, 3H)-2, 5-dione, Methane sulfonic acid and Bioevluation.

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INTRODUCTON

Quinazolinones are fused six membered heterocyclic moiety which possesses two Nitrogens and one Oxygen atom as a ketone position. In 1893, Italian chemist Pietro Biginelli reported on the acid catalyzed cyclocondensation reaction of ethyl acetoacetate, an aldehyde and urea, a procedure known as Biginelli reaction[1]. These are owing to their biological activities e.g. active potential antibacterial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus*

aureusa[2] and also as a calcium antagonist activity[3]. These compounds are widespread due to the diverse range of pharmacological activities e.g, Tyrosina kinase inhibi, Protein[3], Cholecystokinin inhibitory[4], anti inflammatory[5], anti allergy[6], anti malerial[7], anti bacterial[8] and anticancer[9] properties. These compounds occupy a distinct and unique place in the field of medicinal chemistry. Febrifugine was first isolated Quinazolinone alkaloid and its isomer Isofebrifugine exhibited antimalarial activity[10] and Haloguginone is the halogenated derivative of Febrifugine used in veterinary medicine as a coccidiostat[11] and also an important chemical synthon possesses a verity of biological effects including sedative-hypnotic (meethqualone)[12]. Anti anticovulsant[13] and antiussive[14] activities. These compounds having broad spectrum of activities and there is a considerable interest which allows the generations of these compounds. In a recent years, many researchers synthesis of these compounds can be synthesized rapidly.

More recently, the Biginelli reaction has been applied for the synthesis of octahydroquinazolinones, which used cyclicb-diketones instead of open chain dicarbonyl compounds[15]. Literature survey reveals that the synthesis of octahydroquinazolinone derivatives using Trimethylsilylchloride (TMSCl)[16], $VOSO_4$[17], conc. H_2SO_4, conc. HCl, ionic. The corresponding thiazolodine moiety also possesses antibacterial and antifungal activities[18]. Silica sulfuric acid[19] as catalysts. More recently, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones[20], 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, poor yields 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.

MATERIAL AND METHODS

All the chemical, reagents and solvents were purchased from Sigma Aldrich**.** The melting points of the titled compounds were determined by open capillary method and are uncorrected. The purity of the newly 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 and in iodine chamber. 1HNMR and ^{13}CNMR spectra of these compounds were recorded on BRUKER (400 MHz and 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.

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

A mixture of dimedone (1) (10mmol), substituted aromaticaldehyde (2) (10mmol), and urea (3) (15mmol) with the methane sulfonic acid (5mol) without solvent taken in a beaker (capacity 100mL). The reaction was carried out at room temperature. The completion of the reaction was checked by TLC (ethyl acetate/hexane (5:5). The reaction mixture was quenched in crushed ice and then extracted with ethyl acetate and the catalyst was separated by the filtration. The organic layer then washed with a saturated solution of anhydrous sodium bicarbonate twice and organic layer seperated. Organic layer was evaporated under reduced pressure and solid compound was crystallized from absolute ethanol to lead the pure corresponding titled compounds (4a–4h) in moderate to good yields.

Characterization of the synthesized compounds

4-phenyl)-7, 7-dimethyl-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline 2, 5-dione (4a)

Mp: 281-282^{o}C, Yeild-80%, 1HNMR ($CHCl_3$) ppm: 0.91(s, 3H, CH_3), 1.11(s, 3H, CH_3), 2.14(q, J=8.4 Hz, 2H,CH_2), 2.38(q, J=8.0Hz, 2H,CH_2), 5.08(d, J=7.6Hz, 1H, CH), 7.20-7.42(m, 5H, Ar), 8.89(s, 1H, NH), 9.68(s, 1H, NH). ^{13}CNMR ($CHCl_3$) ppm, 193.7, 171.6, 152.6, 150.6, 148.8, 139.2, 128.8, 125.3, 108.4, 51.5, 48.7, 32.9, 27.7, 26.2. Molecular formule: $C_{16}H_{18}N_2O_2$: clculated: C-71.09; H, 6.71; N, 10.36. Found: C, 71.06; H, 6.70; N, 10.39.

4-(4-Chlorophenyl)-7, 7-dimethyl-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline 2, 5-dione (4b)
Mp: 276-278^{o}C, Yeild-86%, ^{1}H NMR (400MHz,$CDCl_3$) δppm: 0.96(s, 3H, CMe); 1.10(s, 3H, CMe); 2.14 (q, J=7.6.2Hz, 2H, CH_2); 2.34(s, 2H, CH2); 5.21 (d, J=7.2Hz, 1H, CH); 7.12-7.41 (m, 4H, Ar); 9.85(s, 1H, NH); 10.24(s, 1H, NH); 13C NMR ((100MHz,$CDCl_3$)δppm:194.6, 172.8, 147.4, 139.5, 132.7, 130.5,129.3, 128.5, 127.2, 107.6, 51.5, 49.6 , 32.5, 28.1, 26.0; LCMS (m/z) 305.54(M+H). Molecular formule: 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.

4-(4-Bromophenyl)-7, 7-dimethyl-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline2, 5-dione (4c):
Mp-282-283^{o}C; Yeild-86%, ^{1}HNMR (400MHz, $CDCl_3$) δppm: 0.94(s, 3H, CMe); 1.10(s, 3H, CMe); 2.20(q, J= 8.8 Hz, 2H, CH2); 2.33(s, 2H, CH2); 5.15(d, J=2.4Hz, 1H, CH); 7.18 (d, J=8.0Hz, 2H, Ar); 7.32(s, J=8.0Hz, 2H, Ar); 9.68(s, 1H, NH); 10.44(s, 1H, NH); ^{13}C NMR (100MHz, ,$CDCl_3$): δ 195.8, 172.7, 149.1 (NC=C), 140.8, 131.4, 129.5, 128.9, 123.0, 108.4, 50.7, 48.2, 32.7, 27.8, 25.9; LCMS (m/z) 349.45.(m+). Molecular formule: C_{17} 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.

7, 7-dimethyl-4-(3, 4, 5-trimethoxyphenyl)-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline-5-dione (4d)
Mp-141-142^{o}C; **Yeild**-84%, ^{1}H NMR (400MHz, $CDCl_3$) δ ppm: 1.03(s, 3H, CMe); 1.14(s, 3H, CMe); 2.15(q, J= 7.6.0Hz, 2H, CH_2); 2.32(q, J=8.0Hz, 2H, CH_2); 3.74(s, 9H, 3(OCH_3)), 4.89(d, J=2.8Hz, 1H, CH); 6.94(s, 2H, Ar); 8.75(s, 1H, NH); 9.79(s, 1H, NH); 13C NMR (100MHz, $CDCl_3$): δ 193.8, 165.9, 153.0, 138.5 , 135.7, 128.8, 122.9, 109.4, 104.8 , 59.6 , 52.9, 50.1, 34.2, 28.2, 27.0; LCMS (m/z) 360.71. Molecular formule: 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.

7, 7-dimethyl 4-(4-hydroxyphenyl)-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline-2, 5-dione (4e)
Mp: 295-296^{o}C; Yeild-88%, ^{1}HNMR (400MHz, $CDCl_3$) δppm: 1.02(s, 3H, CMe); 1.12(s, 3H, CMe); 2.18(q, = 8.4Hz, 2H, CH2); 2.38(q, J=7.6 Hz, 2H, CH_2); 5.01(d, J=7.4Hz, 1H, CH); 6.84-7.08(m, 4H, Ar); 8.45(s, 1H,NH); 10.04(s, 1H, -OH), 10.12(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$): δppm: 192.4, 156.8, 151.7, 149.3, 135.6, 128.8, 118.2, 106.6, 51.8, 48.2, 33.4, 27.7, 26.2. LCMS (m/z)-287.52(M+H). Molecular formule. 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.

7, 7-Dimethyl-4(4-Ethylphenyl)-, 4, 6, 7, 8-Tetrahydro-1H, 3H-quinazoline-2, 5-dione (4f)
Mp. 290- 291^{o}C: Yeild-87%, ^{1}H NMR (400MHz, $CDCl_3$) δppm: 0.92(s, 3H, CMe); 1.06(s, 3H, CMe); 2.14(q, J= 6.8Hz, 2H, CH_2); 2.426(q, J= 7.2Hz, 2H, CH_2); 2.28(s, 3H, CH_3), 4.85(s, 1H, CH); 7.14-7.45 (m, 4H, Ar); 9.86(s, 1H, NH); 10.32(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$): δppm: 193.3, 151.8, 150.5, 147.8, 137.5, 128.8, 125.9, 106.9, 55.7, 49.67 32.8, 28.2, 25.9, 20.6, 19.4. LCMS (m/z)-247.21(M-H). Molecular formule: $C_{14}H_{22}N_2O_2$: Elemental analysis: calculated; C- 67.90; H- 6.68, N- 9.30; Found: C- 67.89, H-6.67; N- 9.35.

7, 7-dimethyl -4-(4-nitrophenyl)-, 4, 6, 7, 8-Tetrhydro-1H, 3H-quinazoline-2, 5- dione (4g): Mp.285-287^{o}C, Yeild-84%, ^{1}HNMR (400MHz, $CDCl_3$) δppm: 1.09(s, 3H, CMe); 1.18(s, 3H, CMe); 2.24(q, J=8.4Hz, 2H, CH_2); 2.44(q, J=7.8Hz,2H, CH_2); 5.31(d, J=7.6Hz, 1H, CH); 7.43-7.88 (m, 4H, Ar); 9.45(s, 1H, NH); 10.08(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δppm 196.4, 153.4, 152.6, 149.4, 144.8, 128.9, 123.9, 106.5, 51.8, 48.4, 32.0, 28.8, 25.9, LCMS (m/z)-316.48(M+H). Molecular formule: $C_{16}H_{17}N_3O_4$; Elemental analysis: calculated: C-60.94; H- 5.43, N- 13.33; Found: C-60.92, H- 5.42; N- 13.38.

4-(2-bromo-3, 4-dimethoxyphenyl)-7, 7-dimethyl, 4, 6, 7, 8-Tetrahydroquinazoline-2, 5-ione (4h)
Mp.298-299^{o}C, Yeild-89%, ^{1}HNMR (400MHz, $CDCl_3$) δppm:0.95(s, 3H, CMe); 1.09(s, 3H, CMe); 2.25(q, J=8.2Hz, 2H, CH_2); 2.46(q, J=7.4Hz,2H, CH_2); 3.79(s, 6H, (OCH_3)2, 4.98(d, J=7.6Hz, 1H, CH); 6.89(d, J=8.8Hz, 1H, Ar-H),6.92(d,J=7.8Hz,1H,Ar-H);7.92(s, 1H, NH); 9.36(s, 1H, NH); ^{13}CNMR(100MHz, $CDCl_3$): δppm197.3, 153.6, 149.8, 146.6, 143.8, 137.6, 125.7, 115.6, 112.7, 106.8, 55.5, 49.6, 45.7, 39.3, 31.7, 27.9, 26.6, LCMS(m/z)-409.37(M+2): Molecular formule: $C_{18}H_{21}NBrN_2O_4$; Elemental

analysis: calculated: C-52.82; H- 5.17, N- 6.84; Found: C- 52.78, H- 5.15; N- 6.96.

4-(2-iodo-3, 5-dimethoxyphenyl)-7, 7-dimethyl-, 4, 6, 7, 8-Tetrahydroquinazoline-2, 5-dione (4i)

Mp-302-304^{o}C, Yeild-87%, ^{1}HNMR (400MHz, $CDCl_3$) δppm: 1.02(s, 3H, CMe); 1.12(s, 3H, CMe); 2.10(q, J=8.6Hz, 2H, CH_2); 2.24(q, J=8.0Hz, 2H, CH_2); 5.05(d, J=7.4Hz, 1H, CH); 6.87(s, 1H, Ar-H), 7.04(s, 1H, Ar-H); 8.45(s, 1H, NH); 9.87(s, 1H, NH); ^{13}CNMR(100MHz, $CDCl_3$) δppm: 198.4, 160.4, 159.7, 150.4, 148.6, 145.8, 123.9, 117.9, 101.5, 56.2, 53.7, 49.4, 46.7, 37.8, 30.5, 27.8, 25.6, LCMS(m/z)-457.17(M+H). Molecular formule: $C_{18}H_{21}IN_2O_4$; Elemental analysis: Calculated: C- 47.38; H- 4.64, N- 6.14; Found: C- 47.36, H- 4.63; N-6.19.

BIOLOGICAL EVALUATION

In-vitro antibacterial activity

Antibacterial Activity

The antibacterial activity of the titled 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 active potent 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 tested compound were evaluated using agar plates possessing Sabourauds dextrose broth for fungi and in nutrient broth for bacteria. The newly synthesized compounds were tested against each microbial species[9-13]. The antibacterial potencies of the newly synthesized have being compared with *Streptomycin* (bacteria) and Fluconazole (fungi). The antimicrobial inhibitions of titled compounds are expressed as the area of zone of inhibition and summarized in Table No.1. This marked and antibacterial activity may be due to the presence of high hydrophobic content of this family of compounds and the quinazaloine 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.

RESULTS AND DISCUSSION

Initially, we found that the best result investigated the reaction of substituted aromatic aldehyde, dimedone and urea in the presence of methane sulfonic acid under solvent free conditions at room temperature (Scheme No.1). The present method doesn't involve any hazardous organic solvents. This catalyst has promising features for the reaction response such as the shortest reaction time, excellent product yields, and simple work-up. The series of tetrahydroquinazalones with substitution in aromatic ring with 4-chloro, 4-Bromo, 3, 4.5-trimethoxy, 4-hydroxy, 4-ethyl, 4-nitro, 2-bromo-3, 4$(OCH_3)_2$, 2-I-3, 5$(OCH_3)_2$ groups were reacted with dimnone and urea presence of methane sulfonic as a catalyst under room temperature condition to prepare a series of tetrahydroquinazalones derivatives (4a-4i). According to the best results were obtained in the presence of methane sulfonic as a catalyst where the products were achieved with high yields and shorter reaction times.

It is observed that various substituted aromatic aldehydes possess electron-releasing or with drawing 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 yield. The microbial activity of titled moiety possesses EWG exhibited more active potent than the EDG of the moiety (Scheme No.1).

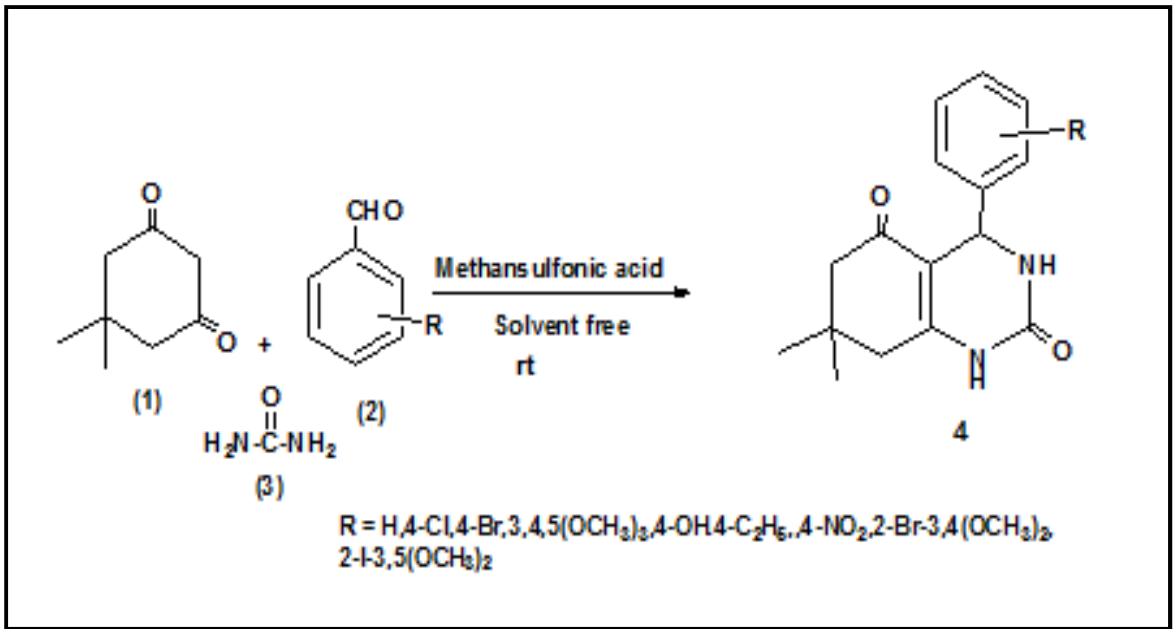
Antibacterial activities of compounds (4a-4i) were measured on three gram negative bacteria (*S. aureus E. coli, S. tyhi, B. substills K. pneumonia and P. aeruginosa*) by disc diffusion method and the minimum inhibitory concentration (MIC) *in-vitro*. Streptomycin was used as the standard antibacterial agent. The results of bioassay are given in Tables No.1.

Compounds 1, 2, 4 and 8-10 exhibited remarkable activity against S. aureus. The compound "4h" showed good activity against *E.coli* and 4i, 4c, 4g showed moderate active potential. The compound

4b exhibit better activity than other derivatives against *S.typhi*. The pathogen *B.substills* showed good activity by "4g" than the remaining derivatives and against all organist tests, in comparison to streptomycin which is a well-known antimicrobial drug. The fungal activity of titled compounds exhibit moderate to good activity against *A.niger* and *C.albicans* compared with Fluconazole.

Table No.1: Antimicrobial activity screening activity synthesized scaffold

S.No	Compound Code	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		S. aureus	*E. coli*	*S. typhi*	*B. substills*	*A. niger*	*C. albicans*
1	4a	10	11	08	6	10	09
2	4b	19	16	20	18	16	15
3	4c	20	19	18	18	17	16
4	4d	13	12	10	13	10	11
5	4e	12	11	12	09	08	10
6	4f	10	13	12	10	09	11
7	4g	21	19	18	20	15	17
8	4h	20	21	19	16	18	16
9	4i	21	20	16	18	18	16
10	streptomycin	25	25	22	22	NA	NA
11	Fluconazole	NA	NA	NA	NA	20	20
12	DMSO	---	----	---	---	---	---



Scheme No.1: The microbial activity of titled moiety possesses EWG exhibited more active potent than the EDG of the moiety

CONCLUSION

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

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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