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An efficient one-pot synthesis, bioassay of 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8- hexahydro-1H-quinazolin-5-ones Promoted PPh_3 as a catalyst

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ABSTRACT:

A straight forward one pot three component synthesis of seven novel derivatives 7**, 7**-dimethyl-4-phenyl-2-thioxo-2,3,4, 6, 7, 8-hexahydro-1H-quinazolin-5-one by a cyclocondensation of dimedone and substitutes aromatic aldehyde with thiourea in the presence of PPh3 as a catalyst with to good yields. All structures of products were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. The antibacterial activity of some synthesized compounds was investigated against *Staphylococcus aureus*), *Staphylococcus epidermidis, Bacillus cereus, Esherichia coli*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa* bacteria. Some of these compounds exhibited a good to significant antibacterial activity. .

KEYWORDS:

Dimedone, substitutedarylaldehydes,7,7-Dimethyl-4-phenyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quinazolin-5-ones , PPh_3, antibacterial activity

1.INTRODUCTION:

An efficient and powerful tools in a modern synthetic organic chemistry is Multi-Component Reactions (MCRs) .They have emerged in synthetic organic chemistry due to their valued features viaz; the opportunity to construct target compounds ,straight forward reaction design, and atom economy, and several diversity elements in a single chemical event. Typically, the purification of products resulting from MCRs. is also simple, and also another important view all organic reagents employed are consumed. MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules [1-7]. Heterocyclic six membered compounds possess a hexahydroquinazolinones are of special interests to their applications in synthetic organic chemistry as well as medicinal chemistry. They are also the basic skeleton of several bioactive compounds. The focus on synthesis of 7, 7-Dimethyl-4-phenyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quinazolin-5-ones and its derivatives have considerable attracted to attention in two decades due to their potential antibacterial activity [9,10] and antioxidant such as antifungal, antibacterial, antitumor and antitubercular. The various classical methods of MCRs of Biginelli reaction involved to improve for synthesis of dimedone, substituted aromatic aldehydes and thiourea. The extension of the Biginelli reaction is employed to use by various Lewis acid catalysts [4- 6] .In order to the extension of the Biginelli reaction due to expensive, harmful and are difficult to handle workup and also sluggish, require more reaction times as well as acidic conditions, give low yields and also suffered from the formation of some side products. These derivatives employed to work on the use of silica-supported reagents [7].TMSCl has attracted our interest for the employed synthesis of the various and considerable attention as an inexpensive and readily available reagent for various organic transformations [8]. Michael addition and cyclodehydration of dimedone with various substituted arylaldhyde the presence of PPh_3, (Scheme -1).Initially, a pilot

reaction was attempted using substituted aromatic benzaldehyde (1), dime done (2) and thiourea (3) in the presence of PPh_3 without any solvent (Scheme-I).

2.METHODS AND MATERIALS:

All the chemical and reagents and solvents were procured from sigma Aldrich chemicals. The melting points of desired synthesized compounds were recorded on Agrawal 535 melting point apparatus and are uncorrected. All the reactions were monitored by thin layer chromatography performed on percolated silica gel 60F254 plates . Compounds were visualized with UV light in iodine chamber. IR spectra were recorded using an Avatar-330 FT-IR spectrophotometer using KBr pellets. NMR spectra of these compounds were recorded on BRUKER 400 MHz spectrometers and ^{13}C NMR was recorded on BRUKER 100 MHz using $CDCl_3$ tetra methyl saline as internal standard. Elemental analyses were carried out in Perkin Elmer 240 CHN elemental analyzer

2.1.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), dimedone (2) (10 mmol) and /thiourea (3) (15 mmol) with the PPh_3 (5 mmol) ethanol as a solvent taken in a beaker (capacity 50 mL).The total mixture arranged on magnetic stirrer and reaction was continued. The completion of the reaction was monitored by TLC (ethyl acetate/hexane,(5:5). The reaction mixture was then extracted with ethyl acetate . The organic layer then washed with water and dried over anhydrous Na_2CO_3. Organic solvent was evaporated under reduced pressure and 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.

2.1.1).7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H- quinazolin-5-one (4a):

Pale yellow solid ; M.p- 207-209^{0}C; Yeild-80%, ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 1.012(s, 3H,), 1.214(s, 3H), 2.145 (q, J= 12.4Hz, 2H, CH_2); 2.256(s, 2H, CH_2), 4.784 (d, J= 8.4Hz,1H, CH); 7.318-7.629 (m, 5H, Ar), 9.546(s, 1H, NH); 10.037(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$) δ ppm: 194.54 , 172.35 , 149.05 , 142.12, 128.53, 127.43, 126.72 , 105.70 , 53.50 , 48.57 , 33.55, 28.86, 26.06 ; LCMS(m/z): 287.57 (M+H); Molecularformule.- $C_{16}H_{18}N_2OS$; Elemental analysis: Calculated: C -67.10; H- 6.33, N- 9.78; Found: C- 67.04, H- 6.31; N- 9.85.

2.1.2)4-(4-Methoxyphenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4b):

Pale yellow solid Mp 214-216^{0}C; Yeild-87%, ^{1}H NMR (400MHz,$CDCl_3$)δ ppm: 0.982(s, 3H) , 1.110(s, 3H), 2.224(q, J=14.0Hz, 2H, CH_2),2.574(s, 2H, CH_2), 3.775(s, 3H, OCH_3),4.717(d, J=4.8Hz, 1H, CH), 6.984(d, J=8.4Hz, 2H, Ar), 7.220(d, J=8.0Hz, 2H, Ar), 9.542(s, 1H, NH); 10.034(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$) δppm: 195.50 , 174.18 , 158.09, 148.28 , 136.50, 128.80, 115.72, 109.57 , 102.53, 55.75 , 52.07 , 50.23 , 32.47, 28.22, 27.02 ; LCMS (m/z): 317.57(M+H); Molecularformule: C_{17} H_{20} N_2 O_2 S: Elemental analysis: calculated C- 64.53; H- 6.37, N-8.85; Found: C- 64.46, H- 6.35; N- 8.95.

2.1.3.)4-(3-Methoxyphenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4c):

Pale yellow solid;Mp-212-2.14^{0}C; Yeild-88%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.967(s,3H); 1.211(s, 3H), 2.122(q, =14.6Hz, 2H, CH_2), 2.524(s, 2H, CH_2), 3.777(s, 3H, OCH_3), 5.021(d, J=4.6Hz, 1H, CH), 6.726-7.252(m, 4H, Ar), 9.751(s, 1H, NH); 10.241(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$)δppm: 195.85 , 173.06, 158.12, 148.26, 144.66, 130.08, 128.64, 119.02, 32.91,28.66, 26.75 ; LCMS (m/z)- 317.87; Molecularformule. C_{17} H_{20} N_2 O_2 S; Elemental analysis: calculated C- 64.53; H-6.37, N- 8.85; Found: C- 64.46, H- 6.35; N- 8.95.

2.1.4)7,7-Dimethyl-2-thioxo-4-p-tolyl-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4d).

Yellow solid, Mp-224- 226^{0}C; Yeild-85%, ^{1}H NMR (400MHz,$CDCl_3$) δppm: 0.945(s, 3H), 1.125(s, 3H), 2.414(q, J=12.4Hz, 2H, CH_2), 2.536(s, 2H, CH_2), 2.730(s, 3H, CH_3), 4.854(d, J=5.6Hz, 1H, CH), 7.218-7.604 (m, 4H, Ar), 9.432(s, 1H, NH); 10.029(s, 1H, NH);^{13}CNMR(100MHz, $CDCl_3$): δppm: 192.54, 174.04 , 148.33 , 140.63, 136.75, 128.08, 126.31 , 108.71, 51.57 , 49.47, 32.11, 28.06, 26.26, 20.25 ;LCMS (m/z)-301.87; Molecularformule: C_{17} H_{20} N_2 O S: Elemental analysis: calculated; C- 67.97; H- 6.71, N- 9.32; Found: C- 67.90, H-6.71; N- 9.45.

2.1.5.) 4-(4-Dimethylamino)-2-hydroxyphenyl)-7, 7-dimethyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quinazolin-5(6H)-one (4e):

Paleyellowsolid; Mp-232-234^{0}C; Yeild-86%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.912(s,3H); 1.117(s, 3H), 2.420(q, J=16.4Hz, 2H, CH_2), 2.453(s, 2H, CH_2); 2.595(s, 6H, NMe_2), 5.011(d, J=6.8Hz, 1H, CH), 6.980-7.425 (m, 3H, Ar),9.773(s, 1H, NH);10.114(s,1H,-OH), 10.442(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δppm 195.09 , 175.02,156.64,150.53, 149.97, 130.81, 125.67, 122.84, 120.03,119.05,49.62,45.37, 37.26, 28.84, 26.66, LCMS(m/z)-345.48.Molecularformule: $C_{18}H_{23}$ N_3 O_2 S; Elemental analysis: calculated: C- 62.58; H-6.71, N- 12.16; Found: C- 65.54, H- 6.71; N- 12.22.

2.1.6.)4-(3-Chlorophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4f):

Pale yellow solid Mp: 236-238^{0}C; Yeild-87%, 1H NMR (400MHz,$CDCl_3$)δppm: 1.097(s, 3H), 1.154(s, 3H); 2.116 (q, J=14.6Hz, 2H, CH_2), 2.328(s, 2H, CH_2), 4.754 (d, J=6.8Hz, 1H, CH), 7.227-7.516(m,4H,Ar-H);9.646(s,1H,NH),10.041(s,1H,NH);^{13}CNMR((100MHz,$CDCl_3$)δppm: 194.25, 175.08, 152.22 , 142.54, 132.08, 128.84, 128.23, 126.91, 124.88 , 106.54 , 53.66 , 48.76 , 32.21 , 28.55, 26.76; LCMS(m/z)- 321.55 (M+H). Molecularformule: C16H17ClN2OS; Elemental analysis: Calculated: C- 59.90; H- 5.34, N- 8.73; Found: C- 59.82, H- 5.32; N- 8.79

2.1.7.)4-(4-Bromophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4g):

Pale yellow solid; Mp-240-242^{0}C; Yeild-88%, 1HNMR (400MHz,CDCl3)δppm: 0.984(s,3H), 1.073(s,3H); 2.147(q, J=14.6Hz, 2H, CH_2); 2.294(s, 2H, CH_2), 4.758(d, J=6.8Hz, 1H, CH), 7.216 (d, J=8.4Hz, 2H, Ar), 7.338(s, J=7.6Hz, 2H, Ar-H); 9.520(s, 1H, NH); 10.130(s, 1H, NH); 13C NMR (100MHz, ,CDCl3) δppm: 196.27 , 173.29 , 147.89, 143.85, 132.07, 130.22, 128.54, 120.34 ,106.56, 51.58, 48.77 , 30.08, 28.95, 26.06 ;LCMS (m/z): 366. Molecularformule Anal. Calcd for C_{16} H_{17} Br N_2 OS: Elemental analysis: calculated: C- 52.61; H- 4.69, N- 7.67; Found: C- 52.60, H- 4.69; N- 7.66.

2.1.8) 4-(4-nitrophenyl)-7, 7-dimethyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5- one (4h):

Brightyellowsolid;Mp.236-238^{0}C;Yeild-84%,^{1}HNMR(400MHz,$CDCl_3$)δppm:1.109(s,3H);1.116 (s,3H), 2.032(q, J=12.6Hz, 2H, CH_2), 2.145(s, 2H, CH_2), 4.589(d, J=8.4Hz, 1H, CH), 7.315-7.762 (m, 4H, Ar), 9.841(s, 1H, NH),10.214(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$) δppm: 195.56,174.28,158.58, 148.09, 145.02, 128.65,128.13, 125.28, 123.74, 105.88, 48.18, 32.56, 28.54,26.96,LCMS(m/z)-330.23(M+H);Molecularformule:$C_{16}H_{17}N_3O_3S$;Elementalanalysis: Calculated: C-57.94; H- 5.17, N- 12.68; Found: C- 57.87, H- 7.16; N- 12.75.

3.ANTIBACTERIAL ACTIVITY:

The antibacterial activity of the titled derivatives specifically 7,7-Dimethyl-4-phenyl-2-thioxo-2,3,4,6,7, 8-hexahydro-1H-quinazolin-5-ones has been examined ***invitro*** for its strong potent active bacterial strains, including S. aureus and Escherichia coli. The test compound's antibacterial potencies have been compared with Streptomycin. The ***invitro*** activities of the screened derivatives were evaluated by using agar plates containing nutrient broth for bacteria. This marked and

antibacterial activity may be exhibited due to the quinazalones ring system and the high hydrophobic content of this family of compounds. The compounds with the quinazalones segment are more active against bacteria, presumably because of the strong interaction of the latter with the agar medium, which hinders their diffusion in agar medium. The antimicrobial inhibitions of test compounds are expressed as the area of zone of inhibition and summarized in Table 1.

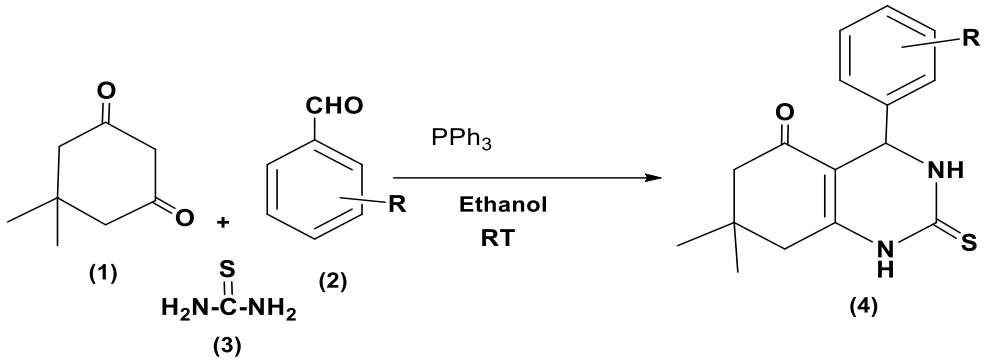
Table-1: *In vitro* antibacterial screening study of the title compounds (4a-4h):

S.No	Compound code	Zone of Inhibition (mm)					
		Gram +ve			Gram –ve		
		S.aureus			E.coli		
		100µg/ml	250 µg/ml	500 µg/ml	100µg/ml	250 µg/ml	500 µg/ml
1	4a	05	08	10	06	07	09
2	4b	12	17	18	18	19	21
3	4c	07	10	18	10	18	19
4	4d	08	14	16	12	15	17
5	4e	16	19	22	11	15	16
6	4f	12	18	21	17	22	24
7	4g	18	20	21	16	22	25
8	4h	08	10	12	12	14	16
Controlee	DMSO	10			10		
STD	Streptomycin	25	25	25	30	30	30

4. RESULTS AND DISCUSSION:

Initially, we observed that the best outcome examined the reaction of substituted aromatic aldehydes, dimedone, and thiourea with triphenyl phosphine at room temperature without the use of ethanol as solvents (Scheme -1). This catalyst has promising features for the reaction performance such as the shortest reaction time, excellent product outcome, easy handling and simple work-up procedure and purification of products by non-chromatographic methods. It is also observed that the different aromatic aldehydes bearing electron-releasing or withdrawing substituents in para-positions lead good yield of the product.

. It is observed that various substituted aromatic aldehydes possess electron-releasing or withdrawing substituents in para-positions lead good yield of the product. The microbial activity of the named moiety possesses EWG exhibited more active potential than the EDG of the moiety. (Table-1) The reusability of the catalyst was investigated; we have not tried this method for aliphatic aldehydes. We found that the reaction of aromatic aldehydes with electron-withdrawing groups was faster than the reaction of aldehydes with electron-donating groups.



(4a-4h)

R = H,3-OCH_3, 4-OCH_3, 4-CH_3, 2-OH-4-$N(CH_3)_2$, 4-Cl,4-Br,4-NO_2

Scheeme-1

5. CONCLUSION:

We believe that this procedure is convenient, economical, and environmentally friendly for the synthesis of the 7,7-Dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8- hexahydro-1H-quinazolin-5-ones derivatives of biological and medicinal most significant . In conclusion, the current methodology is very attractive features such as reduced reaction times, good yields, and ease of product isolation. This is a simple procedure and simple solvent conditions combined with easy recovery and reuse of this catalyst make it an economically and environmentally benign process.

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REFERENCES:

1. Kappe, C.O. \Biologically active dihydripyrimidonesof the Biginelli-type. A literature survey", Eur. J. Med.Chem., 35, pp. 1043-1052 (2000)
2. Yavari, I., Hossaini, Z., Souri, S. and Sey_, S. \Diastereoselectivesynthesis of fused [1,3]thiazolo [1,3]oxazinsand [1,3] oxazino[2,3-b] [1,3]benzothiazoles",Mol. Divers., 13, pp. 439-443 (2009)
3. Shaabani, A., Seyyedhamzeh, M., Maleki, A. andBehnam, M. \A four-component, one-pot synthesisof highly substituted 1,4-dihydro-1,8-naphthyridine-3-carboxamides", Tetrahedron Lett., 50, pp. 6355-6359(2009)
4. Shaabani, A., Bazgir, A. and Teimouri, F. \Ammoniumchloride-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones under solvent-free conditions",Tetrahedron Lett., 44, pp. 857-859 (2003)
5. Shaabani, A., Rahmati, A. and Naderi, S. \A novelone-pot three-component reaction: Synthesis of triheterocyclic4H-pyrimido[2,1-b]benzazoles ring systems",
Bioorg. Med. Chem. Lett., 15, pp. 5553-5557(2005).

6. Quiroga, J., Portillo, S., P_erez, A., G_alvez, J., Abonia,R. and Insuasty, B. \An e_cient synthesis ofpyrazolo[3,4-b]pyridine-4-spiroindolinones by a threecomponentreaction of 5-aminopyrazoles, isatin, andcyclic _-diketones", Tetrahedron Lett., 52, pp. 2664-2666 (2011).
7. Adib, M., Sheibani, E., Bijanzadeh, H.R. and Zhu,L.G. \A new, one-pot, multi-component synthesisof imines of 3-amino-2-arylimidazo[1,2-a]pyridines, 3-amino-2 arylimidazo[1,2-a]pyrazines, and 3-amino-2-arylimidazo[1,2-a]pyrimidines", Tetrahedron, 64, pp.10681-10686 (2008).
8. Rahmati, A. \Synthesis of 4-aryl-3-methyl-6-oxo-4,5,6,7 -tetrahydro-2 H-pyrazolo[3,4-b] pyridine-5-carbonitrile via a one- pot, three-component reaction",Tetrahedron Lett., 51, pp. 2967-2970 (2010).
(9) .Ghorab MM, Adel-Gaward SM and El-Gaby MSA Synthesis and evaluation of some new fluorinated hydroquinazoline derivatives as antifungal agents. *Farmaco*. (2000) 55: 249-255.
10. Hassani, Z.; Islami, M. R.; Kalantari, M. Bio. Org., Med. Chem. Lett. 2006, 16, 4479.