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ONE-POT SYNTHESIS OF 7, 7-DIMETHYL-4-PHENYL-2-THIOXO-2, 3, 4, 6, 7, 8- HEXAHYDRO-1H-QUINAZOLIN-5-ONES BY EMPLOYING KIO5 AS CATALYST

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ABSTRACT

A simple and an efficient work for the synthesis a novel series of derivatives of 7, 7-dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-azone by a one-pot multicomponent cyclocondensation of dimedone and substituted aromatic aldehydes with thiourea in the presence of oxidative catalyst KIO5 in ethanol. This catalyst has beneficial features for the reaction response such as the shortest reaction time, excellent product yields, simple work-up procedure and purification of products by non-chromatographic methods. The newly obtained derivatives can be confirmed by advanced spectroscopic data such as FTIR, 1HNMR, 13CNMR and LCMS and the structural determination of the desired compounds were determined by elemental analysis.

KEYWORDS: Dimedone, substitutedaromaticaldehydes, 7, 7-Dimethyl-4-phenyl-2-thioxo-1, 2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones, KIO_5.

INTRODUCTION

We mainly 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 recent years due to their antibacterial potential activity and antioxidant[1] and as a calcium antagonist.[2] The different conventional methods of one pot multi-component synthesis of Biginelli reaction involved to improve for synthesis of dimedone, substituted aromatic aldehydes and thiourea.[3] The extension of the Biginelli reaction was employed to use by different Lewis acid catalysts.[1-3] In order to the maintain the Biginelli reaction due to

expensive, harmful and are difficult to handle workup and also sluggish, require more reaction times as well as it also have acidic conditions, give low yields and also suffered from the formation of some bi products. These derivatives employed to work on the use of silica-supported reagents.[5] 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.[6] There is no report on the synthesis of 7,7-Dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-onesusingKIO5as iodine catalyst. In this communication, we report a KIO5 catalysed in alcoholic condition simple, efficient and environmentally benign synthesis of 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones (Schemes 1 & 2). During our study we also observed the formation of 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-onesin excellent yields by one-pot Knoevenagel condensation, Michael addition and cyclodehydration of dimedone with various substituted aromatic aldehydes in the presence of KIO5, (Scheme -1).

Initially, we performed a pilot reaction and was attempted using various substituted aromatic benzaldehyde (1), dime done (2) and thiourea (3) in the presence of KIO5 oxidative catalyst (0.5 equiv) with ethanol as solvent (Scheme-I).

This synthesis of 4-aryl-octahydroquinazolin-2,5-dione derivatives by a three-component combination of an aldehydes, dimedone and urea/thiourea has been reported using MCRs in the presence of diverse catalysts including SiO2 –NaHSO4[7], [tbmim]Cl2 /AlCl3[8], silica sulfuric acid[9], thiamine hydrochloride[10], ZrOCl2. 8H2O[11], HCl[12] and H2SO4.[13]

Experimental Section

All the chemical, reagents and solvents were procured from Fine chemicals PVT LTD. The melting points of newly obtained titled product were measured by agrawal melting point instrument and are uncorrected. All the progresses of the reactions were checked by thin layer chromatography performed on percolated silica gel 60F254 plates (Fine chemicals). 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 13C NMR was recorded on BRUKER 100 MHz using CDCl3tetra methyl saline as internal standard. Elemental analyses were carried out in Perkin Elmer 240 CHN elemental analyzer. The determination of the molecular weight of the desired product can be recorded by LCMS.

General procedure for the synthesis of octahydroquinazolinone derivatives

A mixture of substituted aromatic aldehydes (1) (1mol), dimedone (2) (1mol) and /thiourea (3) (2 mol) with the KIO5 (3 mol %) in ethanol as solvent and taken in a beaker (capacity 100 mL). The reaction mixture was arranged on the magnetic stirrer and reaction was carried out at the reflux. After the completion of the reaction, the mixture was examined by TLC as mobile phase (ethyl acetate/hexane: 5: 5). Then the reaction mixture was extracted with ethyl acetate and the catalyst was separated by the filtration of catalyst. The organic layer washed with distilled water and dried over anhydrous Na2SO4. The ethyl acetate layer was evaporated under reduced vacuum and collect crude compound and it 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. The determination of the molecular weight of the desired compound can be recorded by LCMS.

1).7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H- quinazolin-5-one (4a): Whitesolid, Mp241-2420C; Yeild-81%, Rf: 0.45(EtOAc: n-hexane: 5; 8)1HNMR(400MHz, CDCl3) δ ppm: 0.957 (s, 3H, CH3, 0.992 (s, 3H, Me); 2.047 (q, J=10.5, 2H, CH2); 3.125(s, 2H, CH2); 5.057 (s, 1H, CH); 6.925-7.172(m, 2H, Ar-H); 7.389(s, 1H, Ar-H); 8.875(s, 1H, NH); 9.157(s, NH, 1H), 9.794(s, NH, 1H) 13CNMR (100MHz, CDCl3): δppm: 193.44, 174.58, 148.57, 140.28, 128.35, 127.37, 126.20, 104.09, 52.08, 49.75, 32.13, 28.67, 26.68; LCMS(m/z): 287 (M+H).Molecularformule. C16 H18 N2 O S; Elemental analysis: Calculated: C-67.10; H- 6.33, N- 9.78; Found: C- 67.11, H- 6.33; N- 9.77.

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

Whitesolid, Mp-274-2760C; Yeild-78%, Rf: 0.45(EtOAc: n-hexane: 5: 5) 1HNMR(400MHz, CDCl3)δppm: 1.027(s, 3H, CMe); 1.108(s, 3H, CMe); 2.148(q, J=16.0Hz, 2H, CH2); 3.114(s, 2H, CH2); 3.758(s, 3H, OCH3), 5.178(d, J=2.9Hz, 1H, CH); 6.817(d, J=8.7Hz, 2H, Ar-H); 7.207(d, J=8.7Hz, 2H, Ar-H); 9.424(s, 1H, NH); 10.344(s, 1H, NH); 13C NMR (100MHz, CDCl3): δppm: 194.09, 174.84, 159.07, 148.82, 136.07, 128.40, 114.12, 108.57, 100.35, 55.55, 52.06, 50.43, 32.77, 29.52, 27.92; LCMS (m/z): 317.Molecularformule: C17 H20 N2 O2 S: Elemental analysis: calculated C- 64.53; H- 6.37, N-8.85; Found: C- 64.52, H- 6.36; N- 8.86.

3).7, 7-Dimethyl-2-thioxo-4-(2, 4, 6-trimethoxyphenyl)-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5(1H)-one (4c).

White solid, Yeild-90%, RF=0.55(EtOAc: n-hexane: 5: 5);

1HNMR(400MHz, CDCl3)δppm: 9.106(s, 1H, NH), 80574(s, 1H, NH), 6.857-60640(m, 2H, Ar-H), 4.014(s, 1H, C4), 3.694(s, 3H, OCH3), 3.356(s, 6H, 2CH3), 1.576(s, 2H, CH2), 1.182(s, 2H, CH2), 0.877(s, 6H, CH3); 13CNMR(100MHz, CDCl3)δppm: 194.72, 190.08, 156.32, 153.39, 150.77, 128.64, 127.32, 102.64, 52.24, 54.32, 48.45, 44.32, 38.64, 31.72, 28.01.LCMS(m/z)-376.05(M+), Molecular formule: C19H24N2O4S; Elemental analysis: Calculated: C-60.62; H-6.43, N-7.44; Obtained: C-60.55, H-6.41; N-7.53.

4).4-(4-N, N-Diethylamino))-7, 7-dimethyl-2-thioxo-1, 2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5(6H)- one (4d).

White solid, Mp-236-2380C; Yeild-84%, RF=0.50(EtOAc: n-hexane: 5: 5); 1HNMR (400MHz, CDCl3)δppm: 0.879(s, 3H, CMe); 0.981(s, 3H, CMe); 2.057(q, J=10.7Hz, 2H, CH2); 2.187(s, 2H, CH2); 2.347(s, 6H, NMe2), 4.913(d, J=6.4Hz, 1H, -CH-); 6.957-7.147 (m, 2H, Ar); 7.319(s, 1H, Ar-H); 9.446(s, 1H, NH), 9.784(s, 1H, NH); 13C NMR (100MHz, CDCl3): δppm: 195.04, 174.42, 155.46, 149.31, 144.77, 129.71, 128.86, 125.67, 121.94, 121.03, 118.75, 49.56, 45.83, 37.66, 28.74, 26.76, LCMS(m/z)-345.48.Molecularformule: C18H23 N3 O2 S; Elemental analysis: calculated: C- 62.58; H-6.71, N- 12.16; Found: C-65.55, H-6.69; N- 12.20.

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

Palered; Mp-2840C; Yeild-85%, Rf=0.45(EtOAc: n-hexanme: 3: 8); 1HNMR(400MHz, CDCl3) δppm: 0.94(s, 3H, CMe); 1.03(s, 3H, CMe); 2.09(q, J=16.6Hz, 2H, CH2); 2.29(s, 2H, CH2); 4.90(d, J=2.9Hz, 1H, CH); 7.16 (d, J=8.7Hz, 2H, Ar); 7.35(s, J=8.7Hz, 2H, Ar-H); 9.28(s, 1H, NH); 10.30(s, 1H, NH); 13CNMR(100MHz, CDCl3): δ 195.7, 173.9, 148.9, 142.5, 131.7, 131.2, 128.4, 120.4, 106.6, 51.8, 49.6, 31.8, 28.5, 26.6; LCMS (m/z): 366.MolecularformuleAnal. Calcd for C16 H17 Br N2 S; Elemental analysis: calculated: C-52.61; H- 4.69, N- 7.67; Found: C- 52.60, H- 4.69; N- 7.66.

6).4-(7, 7-dimethyl-5-oxo-2-thioxo-1, 2, 3, 4, 5, 6, 7, 8-ocothydroquinazalone-4-yl)benzoic acid(4f)

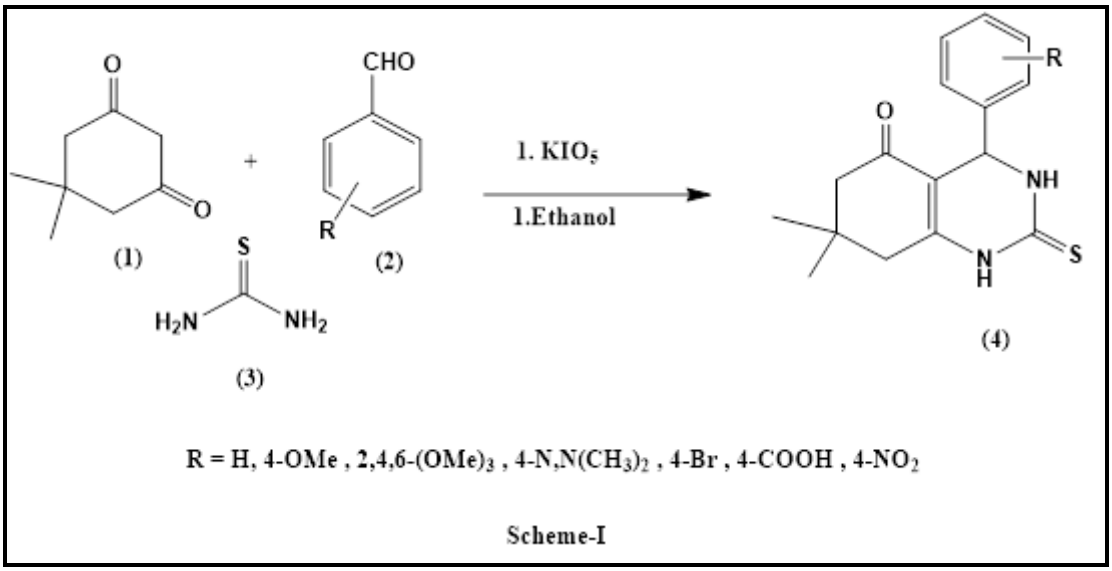
Whitesolid, Yeild-87%, Rf=0.40(EtOAc: n-hexane: 4: 6) 1HNMR(400MHz, CDCl3)δppm: 11.784(s, 1H, COOH), 9.476(s, 1H, NH); 8.974(S, 1H, NH-3); 8.074-7.563(m, 4H, Ar-H); 4.174(s, 1H, C-4), 2.089(s, 2H, CH2); 1.694(s, 2H; CH2); 0.915(s, 3H, CH3); 13CNMR (100MHz, CDCl3): δppm196.62, 191.32, 167.59, 154.66, 145.74, 129.48, 128.74, 127.84, 102.93, 55.86, 49.36, 38.74, 32.85, 28.94; LCMS(m/z)-329.66(M-H).Molecularformule: C17H18 N2 O3S; Elemental analysis: calculated: C- 61.80; H-5.49, N- 8.48; Obtained: C-61.72, H-5.47; N- 8.57.

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

Paleyellow, Mp.272-2740C; Yeild-89%, Rf=0.45(EtOAc: n-hexane: 3: 8)-1HNMR(400MHz, CDCl3)δppm: 1.059(s, 3H, CMe); 1.166(s, 3H, CMe); 2.328(q, J=7.6Hz, 2H, CH2); 2.445(s, 2H, CH2); 5.105(d, J=6.4Hz, 1H, CH); 7.347-7.682 (m, 4H, Ar-H); 9.471(s, 1H, NH); 9.124(s, 1H, NH); 13CNMR(100MHz, CDCl3)δppm: 195.46, 174.88, 158.98, 149.19, 145.95, 128.85, 127.93, 124.78, 124.24, 104.78, 49.68, 33.16, 28.44, 27.46, LCMS(m/z)-330.47.

RESULTS AND DISCUSSION

Initially, we represent that the better result investigated the reaction of substituted aromatic aldehydes, dimedone and thiourea in the presence of oxidative catalyst having iodine such as KIO_5 under solvent as ethanol at reflux (Scheme -1). It was found that various substituted aromatic aldehydes bearing electron- releasing group or seeking group's substituent at Para-positions scaffold good to evolve yield of the desired product. Therefore, we have found that the rate of reaction of aromatic aldehydes containing electron- attracting groups was faster as compared to the rate of reaction of aldehydes having electron releasing groups. It was also observed that the reaction of substituted aromatic aldehydes with thiourea acquired excellent yield.



Scheme-I

Table 1: To optimization of various catalyst effected on 4-OH-3-Acetoxy benzaldehyde.

S.NO	Catalyst (% mol)	solvent	Time(min)	Yield (%)
1	KIO_5	Ethanol	120	92
2	I_2	Ethanol	150	64
3	Cerci ammonium sulphate	Ethanol	120	48
4	Sulphanilic acid	Ethanol	180	58
5	$ZrOCl_2$	Ethanol	150	65
6	Silica per suphuric acid	Ethanol	180	74
7	Camphor sulfonic acid	Ethanol	150	84

The optimization of titled compounds reveals that different catalysts were applied during this reaction. In the same solvent, but different temperature condition and yield different percentages obtained as shown Table-I. The advantages KIO5 as catalyst, which is cheap, easy commercial available, nontoxic, water soluble, easy handling workup.

Table II: To optimization of different solvent effected on 4-OH-3-Acetoxy benzaldehyde.

Entry	Catalyst (3mole %)	solvent	Time(min)	Yield (%)
1	KIO_5	DCM	200	47
2	KIO_5	CH_3CN	150	72
3	KIO_5	CH_3OH	180	64
4	KIO_5	$C_2H_5OH+H_20$	120	92
5	KIO_5	H_2O	24hrs	30

For optimization of various solvents are used in the reaction and also obtained as the reaction product in aqueous alcoholic as solvent compound with the other solvents as shown in table-2.The polar and non-polar solvent are used in this reaction. Out of all solvent working of perfectly functionalized but aqueous alcoholic solvent is excellent soluble and fast reaction compared to other solvents.

Biological Evaluation

Antibacterial Activity

A Cup plate method using HI Media agar medium was employed to examine the antibacterial activity of the synthesized compounds against and Gram-negative bacteria, *Pseudomonas aeruginosa* and *Escherichia coli* and two Gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtili*s. The preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water is done as per the standard procedure.[14] Each test compound (50 mg) was dissolved in DMSO (50 mL, 1000 µg/mL) to prepare a sample solution. Sample volume for all the compounds was fixed at 0.1 mL. The cups were made by scooping out agar

medium with a sterilized cork borer in apetri dish, which was previously inoculated with the microorganisms. The solutions of each desired compound (0.1 mL) was added to the cups and petri dishes and were subsequently incubated at 37 °C for 38 h. Streptomycin and Chloramphenicol were used as reference drugs and DMSO as a control. The zone of inhibition produced by each compound was measured in mm. As shown in the Table-1, the tested compounds showed slightly too moderate antibacterial activity compared to standard drugs against each microorganism.

The evidence of the Table –III, the evaluation of antibacterial study exhibited the compound"4e"most potent activity as compared with standard drug. The derivatives" 4b and 4c" showed that the good activity against tested bacterial strains. The compound "4d" showed moderate active potential and the compounds "4f and 4g"exhibited poor activity.

Table III: Antibacterial activity of the tested compounds.

Zone of inhibition (mm)				
Compound	**Gram negative bacteria**		**Gram positive bacteria**	
	E. coli	***P. aeruginosa***	***B. subtilis***	***S. aureus***
4a	08	10	10	09
4b	16	15	14	16
4c	14	17	15	17
4d	14	13	15	13
4e	**17**	**19**	**16**	**18**
4f	10	13	12	10
4g	07	09	08	10
Control (DMSO)	-	-	-	-
Streptomycin	22	22		
Chloramphenicol			25	25

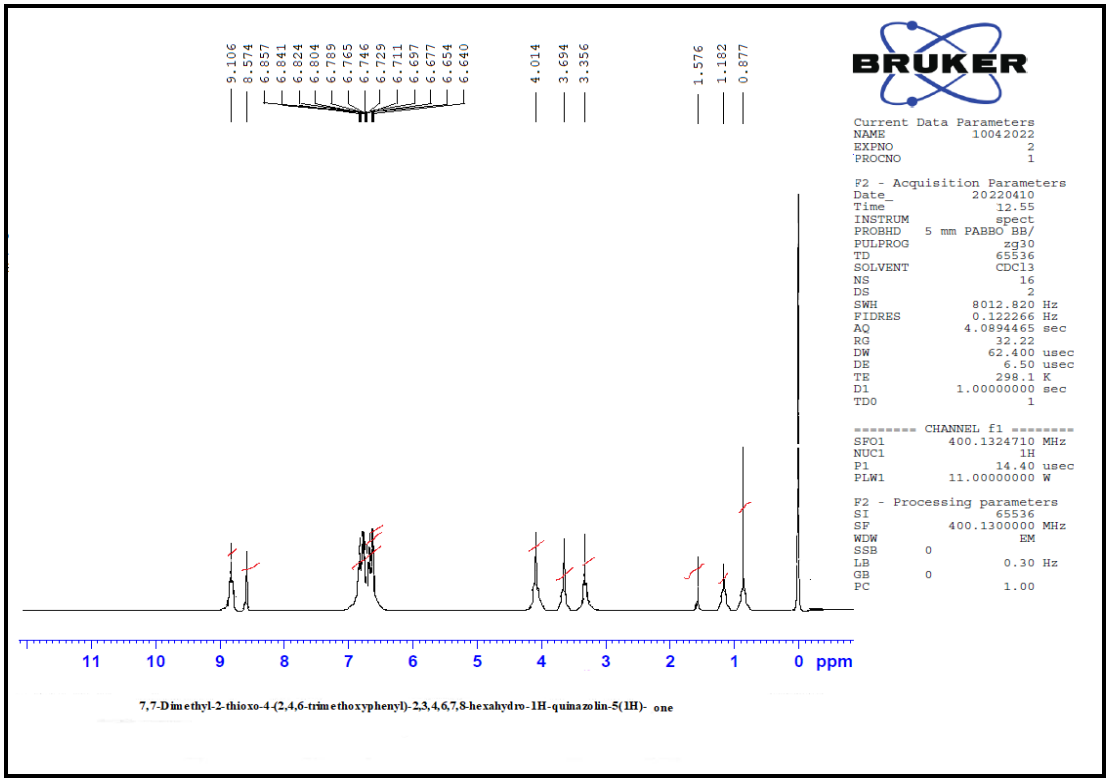
Antifungal Activity

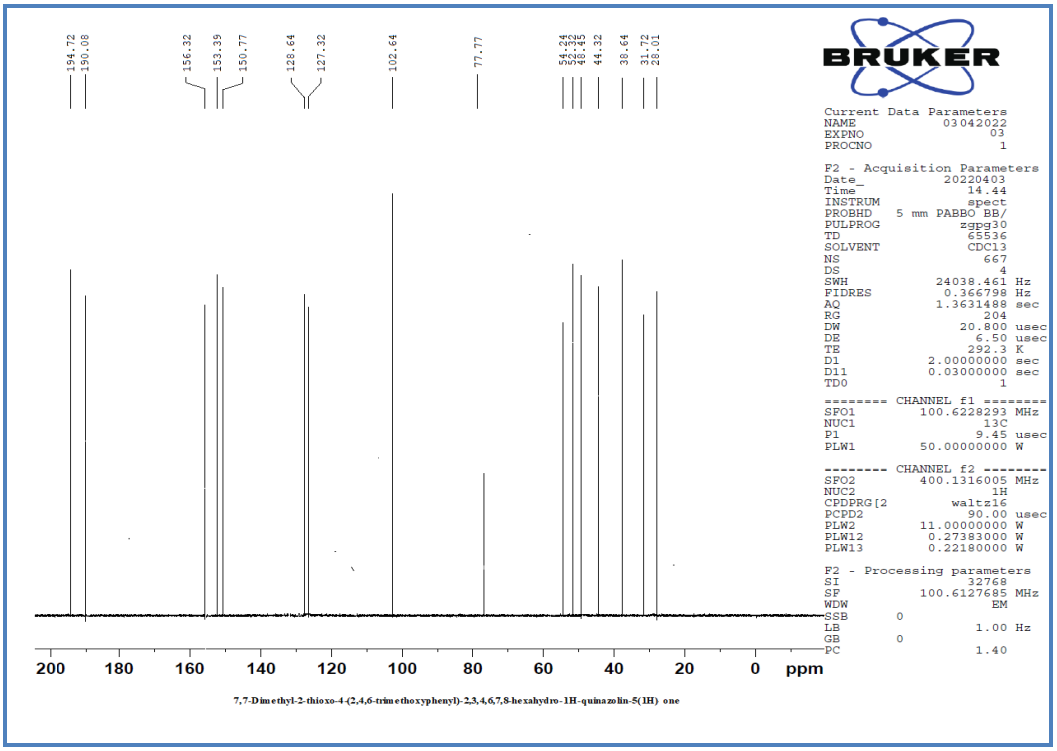
Table-IV: Antifungal activity of the tested compounds.

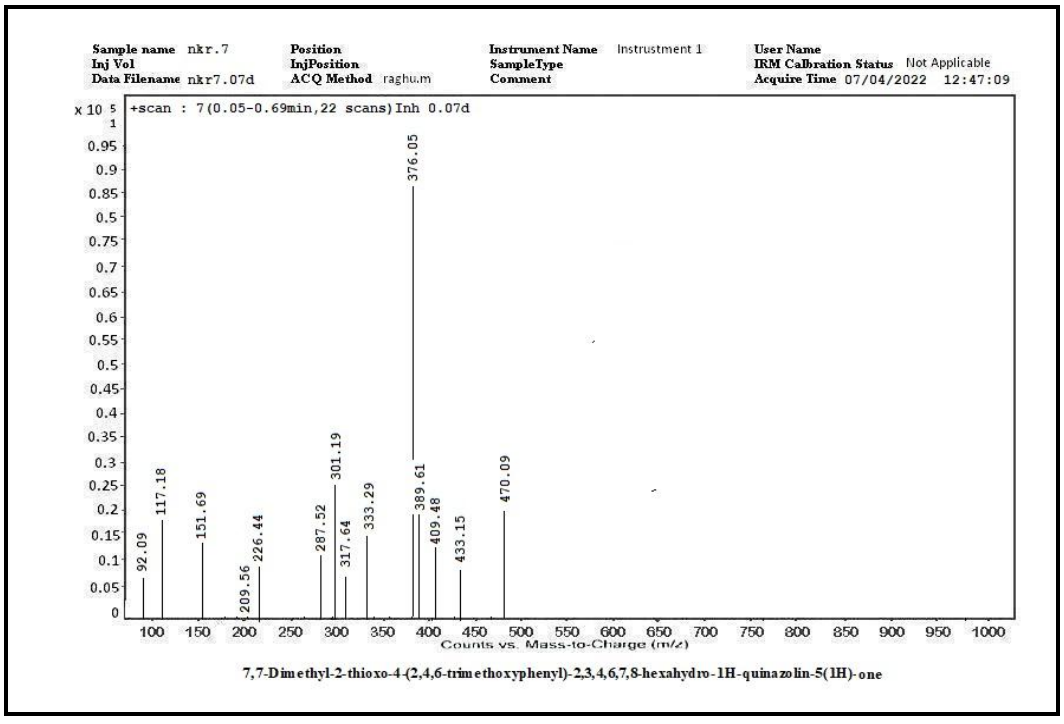
Zone of inhibition (mm)			
Compound	**A. niger**	**C. pannical**	**C. albicans**
4a	05	07	10
4b	12	13	15
4c	17	19	18
4d	15	13	16
4e	**17**	**19**	**18**
4f	08	06	10
4g	05	08	09
Control (DMF)	0	0	0
Ketonozole	25	25	25

The antifungal activity of the desired products was evaluated against three various fungicides. AspergillusNiger, Chrysosporium pannical, and Candida albicans by a filter paper disc technique.[15] the concentration of test compounds was 1000 µg/mL. After treatment for 48 hrs. the zone of inhibition produced by each compound was measured in mm. Ketonozole was used as the standard antifungal agent and DMSO as a control. The results of antifungal activity are depicted in Table 2. Tested compounds showed slight to moderate antifungal activity.

The evidence of the Table –III, the evaluation of antibacterial study exhibited the compound"4e"most potent activity as compared with standard drug. The derivatives" 4b and 4c" showed that the good activity against tested bacterial strains. The compound "4d" showed moderate active potential and the compounds "4f and 4g"exhibited poor activity.







CONCLUSION

In conclusion, efficient catalyst was used for the synthesis of series of titled compounds. It advantage of this having very attractive features such as reduced reaction times, good yields, ease of product isolation. When compared with conventional method as well as with other catalysts which will have wide scope in organic synthesis. This is a simple procedure and

solvent free conditions, which is 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 the 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8- hexahydro-1H-quinazolin-5-ones derivatives of biological and medicinal an importance and also been replaced first of various derivatives of 4-OH, 3-acetoxy benzaldehyde uses KIO_5 as catalyst.

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