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ONE POT BIO ACTIVE SYNTHESIS OF 7, 7-DIMETHYL-4-PHENYL-2-THIOXO-2, 3, 4, 6, 7, 8- HEXAHYDRO-1H-QUINAZOLIN-5-ONES ANALOGOUS PROMOTED BY TFA

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ABSTRACT

A highly efficient methodology has been described for Synthesis of derivatives 7, 7-dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-one derivatives. These derivatives can be synthesized from dime done and substituted aromatic aldehydes with thiourea in the presence of trifluoro acetic acid catalyst with moderate to excellent yields under reflux through condensation followed by cyclization to give desired products. All structures of products were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. In addition to evaluated of the bioevaluation.

KEYWORDS

Dime done, Substituted aromatic aldehydes, 7, 7-Dimethyl-4-phenyl-2-thioxo-1, 2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones, TFA and Bioevaluation.

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INTRODUCTON

Multi component reaction (MCRs) is a most important powerful and efficient tool in a modern synthetic organic chemistry as well as medicinally chemistry. The advantages this reaction in synthetic organic chemistry as well as medicinally chemistry, the valuable characteristics such as the construct titled compounds, straight forward reaction design and atom economy and the purification of target products from MCRs is also simple. MCRs leading to interesting synthesis of heterocyclic moiety and are also particularly useful for the construction 'drug-like 'molecules[1-3]. The six membered heterocyclic molecules are special interest such as a hexahydro quinazolinone in synthetic organic chemistry and in medicinal chemistry. The main

focus on synthesis of series of 7, 7-Dimethyl-4-phenyl-2-thioxo-1, 2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones that have considerable attracted to attention in recent years due to their potent antibacterial activity[4] and antioxidant such as antifungal, antibacterial, antitumor, antitubercular and with broad range applications including anticonvulsant[5], sedative, tranquilizer, analgesic[6,7], antimicrobial[4], anesthetic[8], anticance[9], antihypertensive[10], anti-inflammatory[11], diuretic[12] and muscle relaxant properties[13]. The various methods of MCRs of Biginelli reaction involved to accelerate for Bronsted acids catalyzed acid synthesis of dimedone, substituted aryl aldehydes and thiourea. The utilization of different Lews acid catalyst in the extension of the Biginelli reaction was employed. These derivatives were employed to work on the use of silica-supported reagents. The various organic transformations reaction was employed by the use of TMSCl. There are no report on the synthesis of 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-onesusing nano as a catalyst. Michael addition and cyclodehydration followed by dime done with various substituted arylaldehydes and thiourea in the presence of TFA catalyst (Scheme -1).Initially, a pilot reaction was attempted using substituted aromatic aldehydes (1), dime done (2) and thiourea (3) in the presence of TFA catalyst t (Scheme No.1).

MATERIAL AND METHODS

All the chemical and reagents and solvents were procured from Merck chemicals and before use without further purification. The Agarwal 535 melting point apparatus is used for the determination to measuring temperature of various newly synthesized compounds and are uncorrected. The progression of the reactions was monitored by thin layer chromatography performed on percolated silica gel (Merck chemicals). Compounds were visualized with UV light in iodine chamber. 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.

Experimental Section

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 aromatic aldehydes (1) (10mmol), dime done (2) (10mmol) and /thiourea (3) (15mmol) with thetrifluoroacetic acid catalyst in ethanol as taken in a beaker (capacity 50mL). The total mixture fitted on magnetic stirrer and reaction was proceeding. The completion of the reaction was monitored 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 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.

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

Pale yellow solid, yield-85%,; Rf-0.450 (n-hexane: EtOAc-7:3); ^{1}HNMR (400MHz, $CDCl_3$) δppm: 0.897 (s, 3H, CH_3); 1.11(s, 3H, CH_3); 2.125 (q, J=7.2Hz, 2H, CH_2); 2.231(s, 2H, CH2); 4.895 (d, J=5.8Hz, 1H, CH); 7.012-7.532 (m, 5H, Ar); 9.466(s, 1H, NH); 10.022(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 193.57 , 173.57 , 147.58 , 141.25, 128.59, 127.86, 125.88 , 102.54 , 51.55 , 49.58 , 32.86, 28.20, 26.44.

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

Pale yellow solid, yield-90%; Rf-0.460 (n-hexane: EtOAc-6:43;.1HNMR (400MHz, $CDCl_3$) δppm: 0.895(s, 3H, CH_3); 1.111(s, 3H, CH_3); 2.188(q, J=8.4Hz, 2H, CH_2); 2.501(s, 2H, CH_2); 3.557(s, 3H, OCH_3), 5.010(d, J=8.4Hz, 1H, -CH); 6.882(d, J=8.4Hz, 2H, Ar); 7.224 (d, J=8.4Hz, 2H, Ar); 9.458(s, 1H, NH); 10.023(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δppm: 193.04, 174.70, 158.52, 147.98, 137.51, 128.58, 115.82, 107.57, 100.58, 55.79, 52.74, 50.84, 32.79, 28.29, 26.08 .

4-(3-ethoxy-4-hydroxyphenyl)-7, 7-dimethyl-2-thioxo-1, 2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-one (4c)

Pale yellow solid, yield-92%, Rf-0.445 (n-hexane: EtOAc-5:5); 1HNMR (400MHz, $CDCl_3$) δppm: 0.97(s, 3H, CH_3); 1.11(s, 3H, CH_3); 1.25 (t, 3H, CH_3); 3.46 (q, 2H, -CH_2-), 2.22 (q, =16.1Hz, 2H, CH_2); 2.39 (s, 2H, CH_2); 4.22(d, J=3.6Hz, 1H, CH); 6.70-7.51 (m, 34H, Ar); 9.33 (s, 1H, -OH); 9.73(s, 1H, NH); 10.26(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$): δppm: 193.69, 173.16, 159.84, 147.88, 145.73, 139.18, 132.75, 119.86, 116.73, 115.55, 101.84, 60.89, 50.94, 47.78, 36.79, 30.76, 26.53, 13.27.

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

Pale yellow solid, yield-88%, Rf-0.450 (n-hexane: EtOAc-7:3); 1HNMR (400MHz, $CDCl_3$) δppm: 1.085(s, 3H, CH_3); 1.215(s, 3H, CH_3); 2.026(q, J=8.4Hz, 2H, CH_2); 2.326(s, 2H, CH_2); 2.754 (s, 6H, NMe_2), 4.294(d, J= 7.6Hz, 1H, -CH); 7.109-7.249 (m, 3H, Ar); 9.454(s, 1H, NH); 9.587 (s,1H,-OH), 10.136(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δppm 193.59, 174.22, 158.06, 151.76, 149.52, 130.94, 128.27, 122.29, 121.54, 120.15, 49.28, 46.33, 38.46, 28.68, 26.59.

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

Pale yellow solid, yield-89%; Rf-0.470 (n-hexane: EtOAc-5:5);. ^{1}HNMR (400MHz, $CDCl_3$) δppm: 0.954 (s, 3H, CH_3); 1.105(s3H, CH_3); 2.519 (q, J=7.6Hz, 2H, CH_2); 2.240 (s, 2H, CH_2); 5.017(d, J=6.8Hz, 1H, CH); 7.036-7.415 (m, 4H, Ar); 9.174 (s, 1H, NH); 10.034 (s, 1H, NH); ^{13}CNMR ((100MHz, $CDCl_3$) δppm: 195.25, 173.62, 151.77, 142.84, 133.60, 129.75, 126.93, 127.54, 125.58 , 104.84 , 52.58 , 50.36 , 32.67, 28.09, 25.96.

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

Paley brown solid, yield-89%, m.p-251-253^{o}C; Rf-0.440 (n-hexane: EtOAc-5:5); ^{1}HNMR, (400MHz, $CDCl_3$) δppm: 0.948 (s, 3H, CH_3); 1.109(s, 3H, CH_3); 2.114 (q, J=8.4Hz, 2H, CH_2); 2.235(s, 2H, CH_2); 5.008 (d, J=7.2Hz, 1H, -CH); 7.220 (d, J=8.4Hz, 2H, Ar); 7.544(s, J=7.6Hz, 2H, Ar); 9.772(s, 1H, NH); 10.123(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δ 195.21, 173.56, 147.04, 141.57, 132.27, 130.22, 128.88, 121.45, 104.56, 52.40, 49.42, 32.54, 28.46, 25.19.

4-(2-iodo-3, 5-dimethoxy phenyl)-7, 7-dimethyl-2-thioxo-1, 2, 3, 4, 7, 8-hexahydro quinazolne-5(6H)-one (4g)

Pale yellow solid, yield-90%,; Rf-0.480 (n-hexane: EtOAc-6:4); ^{1}HNMR (400MHz, $CDCl_3$) δppm: 0.892 (s, 3H, CH_3); 1.213(s, 3H, CH_3); 2.124 (q, J=7.4Hz, 2H, CH_2); 2.084(s, 2H, CH_2); 3.676(s, 6H, ($2OCH_3$)), 5.107(d, J=7.2Hz, 1H, -CH); 6.894(s,1H, Ar); 7.102(s,1H, Ar); 9.884(s, 1H, NH); 10.213(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δppm: 195.56, 169.58, 156.87, 151.57, 147.82, 119.58, 116.76, 115.93, 105.84, 55.52, 54.68, 51.83, 48.97, 38.73, 28.96, 25.73.

4-(7, 7-dimethyl-5-oxo-2-thioxo-1, 2, 3, 4, 7, 8-ocatahydroquinazolne-4-yl) benzonitrile (4h)

Pale yellow solid, yield-90%, Rf-0.480 (n-hexane: EtOAc-5:5); 1HNMR (400MHz, CDCl3) δppm: 1.107(s, 3H, CH_3); 1.216(s, 3H, CH_3); 2.132(q, J= 8.4Hz, 2H, CH_2); 2.243(s, 2H, CH_2); 5.02 (d, J=8.8Hz, 1H, -CH); 7.329-7.586 (m, 4H, Ar); 9.552(s, 1H, NH); 10.129(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$): δppm 195.92, 173.89, 159.55, 149.62, 145.54, 130.46, 128.82, 120.78, 112.54, 104.77, 52.93, 49.72, 38.86, 29.44, 29.54.

Biology

Antibacterial Activity

The antimicrobial activity of the titled compounds showed such as 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8- hexahydro-1H-quinazolin-5-ones and its derivatives have being screened in vitro for its bacterial strains such as, *E.coli, P.aeruginosa, B.substilis, B.megaterium, A.niger and C.albicans*. The test compound was screened using agar plates containing in nutrient broth for bacteria *in vitro* activities. The test compound was screened against each microbial species[8-11]. The antibacterial potencies of the test compound have being compared with *Streptomycin.* The antimicrobial inhibitions of test compound are expressed as the area of zone of inhibition and summarized in Table No.1 and Table No.2. 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 containing 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

We observed that an important result in investigated the reaction of substituted aromatic aldehydes, dime done and thiourea in the presence of trifluoro acetic acid catalyst under solvent free conditions at room temperature (Scheme No.1). The advantages this catalyst used for in the reaction, which is response carried out easy work-up, the low reaction time, good yields and purification of titled compound by non-chromatographic methods. It is also identified that various substituted aromatic aldehydes having electron withdrawing and electron-releasing substituents in para-positions leads better yield than that of ortho substituents.

Therefore, we observed that the reaction of aromatic aldehydes having electron-withdrawing groups was faster rate of reaction as compared to the reaction of aldehydes possessing electron realsing groups. The reusability of this catalyst was investigated; we have not tried this method for aliphatic aldehydes. The antimicrobial activity of titled compounds possesses EWG exhibited more active potent than the EDG of the moiety (Table No.2).

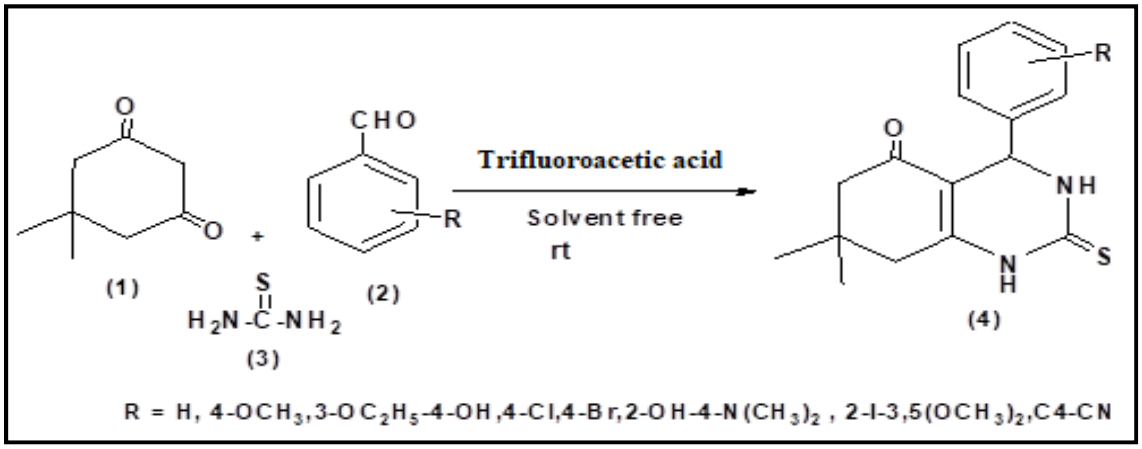
Table No.1: Synthesis of titled derivatives catalyzed by TFA catalyst solvent-free conditions

Entry	AR	Molecular Formula	Time[a] (min)	Yield[b] (%)	MW g/mol	m.p (^oC) Lit)
4a	C_6H_5	$C_{16}H_{18}N_2OS$	75	85	286.07	285-286^oC
4b	4-OH-C_6H_4	$C_{17}H_{20}N_2O_2S$	120	90	317.25	274-276^oC
4c	3-OC_2H_5-4-OH-C_6H_3	$C_{18}H_{22}N_2O_3S$.	120	92	365.12 (M-H).	273-274^oC
4d	4-Cl-C6H4	$C_{16}H_{17}ClN_2OS$	150	88	321.33	274-276^oC (Lit 275-276^oC
4e	4-Br-C_6H_4	$C_{16}H_{17}BrN_2OS$	150	89	366.56	284^oC
4f	2-OH-4-N$(CH_3)_2$-C_6H_3	$C_{18}H_{23}N_3O_2S$	120	89	345.44	275-277^oC
4g	2-I-3,5-$(OCH_3)_2$-C_6H_3	$C_{18}H_{21}IN_2O_3S$.	150	90	472.09	275-276^oC
4h	4-CN-C_6H_4	$C_{17}H_{17}N_3OS$.	150	90	310.87 (M-H)	269-271^oC

Reaction was continued until the TLC shown the starting materials disappeared, isolated yield

Table No.2: *In vitro* antibacterial screening study of the title compounds 4(a-h)

S.No	Compound code	Zone of Inhibition against(mm)					
		E.coli	***P.aeruginosa***	***B.subtilis***	***B.megaterium***	***A.Ngier***	***C.albicans***
1	4a	07	09	08	08	07	09
2	4b	21	20	19	26	14	14
3	4c	21	22	20	21	15	16
4	4d	19	20	20	21	14	15
5	4e	14	12	20	20	10	10
6	4f	15	14	15	15	12	13
7	4g	16	14	15	15	17	17
8	4h	15	12	19	20	17	16
Controle	DMSO	10			10		
STD	Streptomycin	25	25	25	25	20	20



Scheme No.1

CONCLUSION

In conclusion, an efficient catalyst for the synthesis of titled compounds. The present methodology is very interest and attractive features such as reduced 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 *the* 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones derivatives of biological and medicinal importance.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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