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### RESEARCH ARTICLE

#### MICROWAVE ASSISTED ONE POT SYNTHESIS OF 5-UNSUBSTITUTED-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES UNDER SOLVENT FREE CONDITION:BIGINELLI REACTION.

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#### Abstract

3,4-dihydro-6-(2,4-dihydroxyphenyl)-4-phenylpyrimidin-2(1H)-one (4) has been synthesized by the condensation of 2,4-dihydroxybenzaldehyde, acetophenone and urea with a catalytic amount of  $ZnI_2$  under microwave irradiation. In this paper the synthesis, mass spectral analysis and anti-inflammatory activities of (3,4-dihydro-6-(2-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-one (1) 6-(4-(dimethylamino)phenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-one (2), 3,4-dihydro-6-(3-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-one (3), 3,4-dihydro-6-(2,4-dihydroxyphenyl)-4-phenylpyrimidin-2(1H)-one (4), 6-(3-ethoxy-2-hydroxyphenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-one (5), 3,4-dihydro-6-(4-nitrophenyl)-4-phenylpyrimidin-2(1H)-one (6), 6-(2,3-diethoxyphenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-one (7), 3,4-dihydro-6-(2-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-thione (8), 6-(4-(dimethylamino)phenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-thione (9), 3,4-dihydro-6-(2,4-dihydroxyphenyl)-4-phenylpyrimidin-2(1H)-thione (10), 3,4-dihydro-6-(4-nitrophenyl)-4-phenylpyrimidin-2(1H)-thione (11), 6-(2,3-diethoxyphenyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-thione (12) are being reported.

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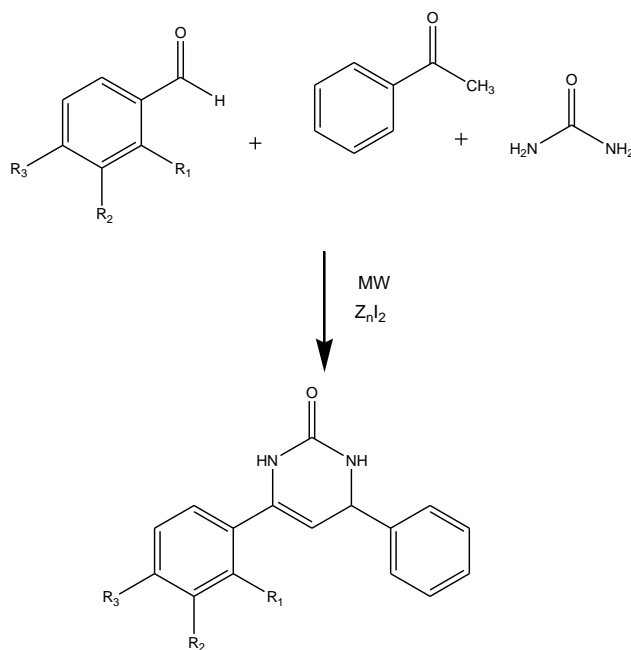
#### Introduction:-

BIGINELLI REACTION IS A SIMPLE ONE POT CONDENSATION OF AN ALDEHYDE, KETOESTER, UREA IN A SOLVENT SUCH AS ETHANOL USING A STRONGLY ACIDIC CATALYST, THAT IS, HYDROCHLORIC ACID TO PRODUCE 3,4-DIHYDROPYRIMIDIN-2-(1H)-ONES, WHICH WAS REPORTED BY BIGINELLI<sup>1</sup>. HOWEVER THE YIELD OF PRODUCTS WERE VERY LOW (20-50%). FROM THEN ON, MANY NEW TECHNIQUES, SUCH AS MICROWAVE ASSISTED SYNTHESIS TECHNIQUES, IONIC LIQUIDS ULTRASOUND IRRADIATION, SOLVENT-FREE TECHNIQUES AND MUCH NEW CATALYST, SUCH AS  $INBR_3$ ,  $ZrCl_4$ ,  $BiCl_3$  ETC, WERE USED TO IMPROVE THIS TRANSFORMATION. IN SPITE OF THEIR POTENTIAL UTILITY, MANY OF THESE METHODS INVOLVE EXPENSIVE REAGENTS, STRONGLY ACIDIC CONDITIONS, LONG REACTION TIMES, HIGH TEMPERATURE AND STIOCHIOMETRIC AMOUNTS OF CATALYSTS AND UNSATISFACTORY YIELDS. THE FIRST BIGINELLI LIKE REACTION WAS CONDUCTED IN  $CH_3CN$  BY USING ALDEHYDES, KETONES, AND UREA AS SUBSTRATES AND  $FeCl_3 \cdot 6H_2O$  AND  $TMSCL$  AS CATALYSTS, WHICH REMARKABLY BROADENED THE BIGINELLI REACTION<sup>2</sup>. HOWEVER, OF SUFFERED FROM ITS DRAWBACKS, ESPECIALLY THE USE OF HIGHLY TOXIC ORGANIC SOLVENT, LONG REACTION TIME (12H) AND STIOCHIOMETRICTMSCL. MANY CATALYSTS OR PROMOTERS, SUCH AS  $CH_3COOH$ ,

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$\text{Fe}_2(\text{SO}_4)_3$ ,  $\text{MgSO}_4$ ,  $\text{HCl}$ ,  $\text{H}_2\text{SO}_4$ , ETC, WERE USED TO EXPLORE THE REACTION UNDER SOLVENT-FREE, MICROWAVE ASSISTED CONDITIONS. THESE RESULTS SUGGESTS THAT MOST OF THE LEWIS ACID AND BRONSTED ACIDS COULD PROMOTE THE REACTION, BUT THE YIELDS ARE NOT SO HIGH<sup>3</sup>. IN COMPARISON WITH OTHER CATALYSTS, THE USE OF 1.5 MMOL OF  $\text{ZnI}_2$  COULD MAKE THE YIELD REACH 48% UNDER MICROWAVE IRRADIATION<sup>4</sup>. THE REASON FOR  $\text{ZnI}_2$  BEING THE BEST CATALYST MAY BE STRONGLY ACIDIC CHARACTER<sup>5</sup>. IN ORDER TO EXAMINE THE SUBSTRATE SCOPE OF THIS BIGINELLI-LIKE REACTION, VARIOUS AROMATIC ALDEHYDES WITH DIFFERENT SUBSTITUENT USING  $\text{ZnI}_2$  WERE USED UNDER THE OPTIMIZED REACTION CONDITION TO SYNTHESIZE A SERIES OF 5-unsubstituted-3,4-dihydropyrimidin-2(1H)-ones.



Compound no.	-R <sub>1</sub>	-R <sub>2</sub>	-R <sub>3</sub>
1	-OH	-H	-H
2	-H	-H	-N(CH <sub>3</sub> ) <sub>2</sub>
3	-H	-OH	-H
4	-OH	-H	-OH
5	-OH	-OC <sub>2</sub> H <sub>5</sub>	-H
6	-H	-H	-NO <sub>2</sub>
7	-H	-OC <sub>2</sub> H <sub>5</sub>	-OC <sub>2</sub> H <sub>5</sub>
8	-OH	-H	-H
9	-H	-H	-N(CH <sub>3</sub> ) <sub>2</sub>
10	-OH	-H	-OH
11	-OH	-H	-OC <sub>2</sub> H <sub>5</sub>
12	-H	-OC <sub>2</sub> H <sub>5</sub>	-OC <sub>2</sub> H <sub>5</sub>

#### Experimental:-

All reactions were performed on a domestic microwave oven (Power 1200 W). All reactants were obtained from commercial sources and freshly distilled prior to use. Melting points were taken in an electrically heated instrument and are uncorrected. Compounds were routinely checked for their purity on silica gel TLC plates and the spots were visualized by iodine vapors. IR spectra were recorded on Shimadzu 8201 PC FTIR spectrometer. PMR spectra were recorded on Bruker DRX 300 mhz FT NMR spectrometer using TMS as internal reference and chemical shift values are expressed in  $\delta$  units. Mass spectra were run on Jeol SX - 102 spectrometer.

#### General Procedure:-

For the synthesis of compounds 1-12, a mixture of the appropriate aldehyde, acetophenone and urea or thiourea in equimolar concentration with a catalytic amount of  $\text{ZnI}_2$  in a 100ml glass tube was irradiated in a microwave oven in

bursts of 15-20 seconds. The reaction was monitored by TLC. After the reaction was completed, distilled water was added into the flask and stirred for several minutes and then filtrated through a sintered funnel to afford crude product, which was further purified by recrystallization (etoh). Reaction details are given in Table 1.

**Table 1:-Reaction Details.**

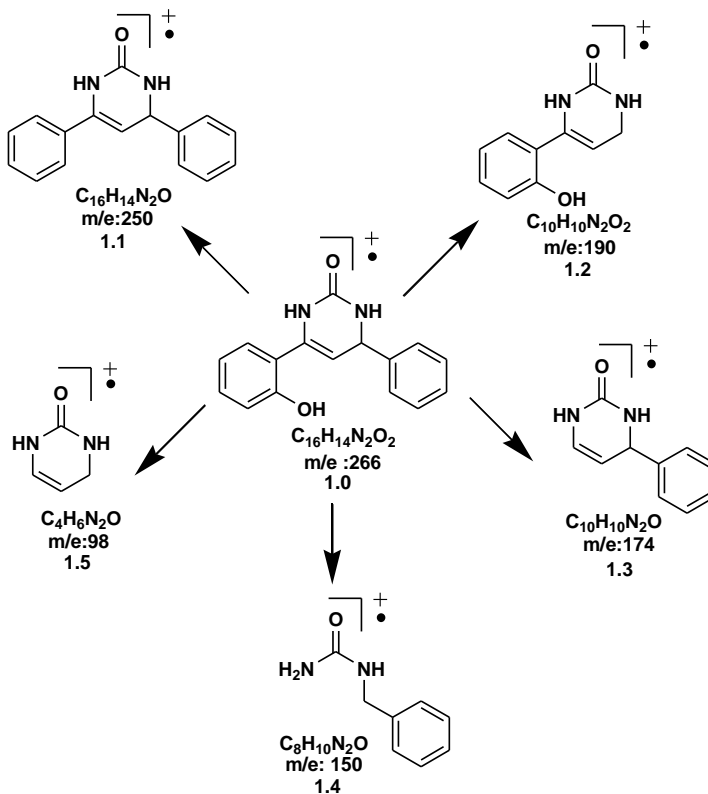
No.	Aldehyde	Amide	Time (Minutes)	Yield (%)	Mp ( $^{\circ}$ C)
1	2-hydroxybenzaldehyde	Urea	6	65.5	250
2	4-dimethylaminobenzaldehyde	Urea	5	63.0	240
3	3-hydroxybenzaldehyde	Urea	6	75.2	232
4	2,4-dihydroxybenzaldehyde	Urea	6	55.0	265
5	3-ethoxy,2-hydroxybenzaldehyde	Urea	7	68.3	215
6	4-nitrobenzaldehyde	Urea	8	66.1	227
7	3,4-diethoxybenzaldehyde	Urea	5	70.0	260
8	2-hydroxybenzaldehyde	Thiourea	6	74.8	255
9	4-dimethylaminobenzaldehyde	Thiourea	6	65.0	242
10	2,4-dihydroxybenzaldehyde	Thiourea	5	67.0	234
11	3-ethoxy,2-hydroxybenzaldehyde	Thiourea	6	78.0	230
12	2,3-diethoxybenzaldehyde	Thiourea	5	76.0	222

**Table 2:-Spectral Data.**

	Mass (m/z)	$^1$ H NMR Data (dmsod <sub>6</sub> )
1	266,250,190,174,150,98	7.06-7.14(m, 5H, arh), 6.61-7.04(m, 4H, arh), 6.0(s, 1H, NH), 5.94(s, 1H, CH).
2	293,250,217,174,98	7.06-7.14(m, 5H, arh), 6.61-7.04(m, 4H, arh), 6.0(s, 1H, NH), 5.94(s, 1H, CH), 4.87(s, 1H, CH), 2.85(s, 3H, CH <sub>3</sub> ).
3	266,250,198,174,98	7.06-7.14(m, 5H, arh), 6.61-7.04(m, 4H, arh), 6.0(s, 1H, NH), 5.94(s, 1H, CH), 4.87(s, 1H, CH).
4	282,266,226,250,206,174,98	7.06-7.14(m, 5H, arh), 6.15-6.96 (m, 3H, arh), 6.5(s, 1H, CH), 5.0(s, H, aroh), 6.0(s, 1H, NH), 4.59(s, 1H, CH).
5	310,294,266,250,234,174,98	7.06-7.14(m, 5H, arh), 6.48-6.69 (m, 3H, arh), 6.0(s, 1H, NH), 5.56(s, 1H, CH), 5.0 (s, H, aroh), 3.98(q, 2H, CH <sub>2</sub> ), 1.33(t, 3H, CH <sub>3</sub> ).
6	295,250,219,174,98	7.56-8.14(m, 4H, arh), 7.06-7.14 (m, 5H, arh), 6.23(s, 1H, CH) 6.0(s, 1H, NH).
7	338,294,233,261,174,98	7.06-7.14(m, 5H, arh), 6.61-6.75 (m, 3H, arh), 6.0(s, 1H, NH), 5.56(s, 1H, CH), 3.98(q, 2H, CH <sub>2</sub> ), 1.33(t, 3H, CH <sub>3</sub> ).
8	282,266,206,190,114	7.06-7.14(m, 5H, arh), 6.77-7.13 (m, 4H, arh), 6.5(s, 1H, CH), 5.0(s, 1H, aroh), 2.0(s, 1H, NH).
9	309,265,233,190,114	7.06-7.14(m, 5H, arh), 6.54-7.12(m, 4H, arh), 4.59(s, 1H, CH), 2.85(s, 3H, CH <sub>3</sub> ), 2.0(s, 1H, NH).
10	298,282,266,222,206,114	7.06-7.14(m, 5H, arh), 6.24-6.96 (m, 3H, arh), 6.5 (d, 1H, CH), 5.0(s, 1H, aroh), 4.59(d, 1H, CH), 2.0(s, 1H, NH).
11	326,310,282,250,190,114	7.06-7.14(m, 5H, arh), 6.48-6.69 (m, 3H, arh), 6.5(d, 1H, CH), 5.0(s, 1H, aroh), 3.98(q, 2H, CH <sub>2</sub> ), 2.0(s, 1H, NH), 1.33(t, 3H, CH <sub>3</sub> ).
12	352,325,310,282,278,190,114	7.06-7.14(m, 5H, arh), 6.61-6.75 (m, 3H, arh), 6.5 (d, 1H, =CH), 5.56(s, 1H, CH), 4.59(d, 1H, CH), 3.98(q, 2H, CH <sub>2</sub> ), 2.0(s, 1H, NH), 1.33(t, 3H, CH <sub>3</sub> ).

#### Mass Spectral Analysis:-

Mass spectral studies of 3,4-dihydro-6-(2-hydroxyphenyl)-4-phenylpyrimidin-2(1H)-one has shown variation in fragmentation only due to differently substituted phenyl ring, hydroxyl group, ethoxy group, nitro group, dimethylamino group. All the compounds in general have exhibited a similar pattern of fragmentation (scheme 2). The mass and NMR spectral data of the compounds are given in Table 2.

**Biological activity:-**

The compounds were tested for their anti-inflammatory activities against carrageenin induced rats paw edema using the method described<sup>6</sup>. The results are summarized in tables

**Table 3:-**Percentage edema growth relative to control at different time intervals (mean  $\pm$  SEM).

Group	0 (min)	30 (min)	90 (min)	180 (min)
Control	100 $\pm$ 0	130.1 $\pm$ 6.54 (30.1)	138.7 $\pm$ 4.47 (38.7)	122.3 $\pm$ 5.17 (22.3)
1	100 $\pm$ 0	103.9 $\pm$ 2.59 (3.9)	106.2 $\pm$ 3.98 (6.2)	99.6 $\pm$ 2.54 (0.4)
2	100 $\pm$ 0	114.5 $\pm$ 3.90 (2.65)	123 $\pm$ 2.20 (2.65)	103 $\pm$ 4.5 (2.6)
3	100 $\pm$ 0	115.6 $\pm$ 2.48 (5.2)	120 $\pm$ 7.65 (25.5)	123 $\pm$ 8.56 (15.5)
4	100 $\pm$ 0	106.5 $\pm$ 3.67 (6.5)	118.4 $\pm$ 3.86 (18.4)	121.4 $\pm$ 4.55 (21.4)
5	100 $\pm$ 0	133.9 $\pm$ 7.56 (33.9)	144.5 $\pm$ 6.54 (46.5)	133.6 $\pm$ 7.58 (33.6)
6	100 $\pm$ 0	118.9 $\pm$ 3.56 (23.9)	124.5 $\pm$ 5.54 (6.2)	123.6 $\pm$ 7.58 (30.6)
7	100 $\pm$ 0	108.1 $\pm$ 7.05 (44.2)	114.8 $\pm$ 6.80 (14.5)	123.8 $\pm$ 3.20 (23.6)
8	100 $\pm$ 0	124.9 $\pm$ 2.25 (23.2)	134.9 $\pm$ 6.50 (16.4)	143.3 $\pm$ 8.20 (25.7)
9	100 $\pm$ 0	116.3 $\pm$ 2.30 (14.3)	123.3 $\pm$ 4.32 (23.2)	132.2 $\pm$ 6.36 (14.8)
10	100 $\pm$ 0	126.8 $\pm$ 3.56 (14.8)	127.7 $\pm$ 3.33 (26.6)	130.1 $\pm$ 1.30 (42.3)
11	100 $\pm$ 0	113.5 $\pm$ 2.20 (18.2)	131.5 $\pm$ 5.50 (15.5)	136.0 $\pm$ 5.30 (16.4)
12	100 $\pm$ 0	123.5 $\pm$ 3.50 (15.6)	134.6 $\pm$ 8.56 (18.5)	141.7 $\pm$ 7.23 (31.2)
Ibuprofen	100 $\pm$ 0	101.7 $\pm$ 2.11	108 $\pm$ 3.27	11.6 $\pm$ 4.19

**Table 4:-**Anti-inflammatory activity screening data of the compounds.

Compound No.	Mean Difference	Percent Activity(100mg/Kg)
1	35.20	59
2	26.14	36
3	25.63	35
4	25.63	37

5	24.35	39
6	23.18	40
7	17.73	49
8	32.50	52
9	23.18	52
10	23.50	35
11	21.19	32
12	22.01	45

**Acknowledgement:-**

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