



# Synthesis of Some New 3, 5-Disubstituted Pyrimidine and Thiopyrimidine Derivatives as Potent Antimicrobial Agents

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## Abstract:

1-(5-Chloro-2-hydroxyphenyl)-ethanone (1a) was prepared from 2-chlorophenol through multi-step reaction. Compound (1a) reacts with different aryl aldehyde in the presence of NaOH (40%) to gives 1-(5-chloro-2-hydroxyphenyl)-3-(4-substitutedphenyl)-prop-2-en-1-one (2a-e). 4-(5-chloro-2-hydroxyphenyl)-6-(4-substitutedphenyl)-pyrimidin-2-(1H)-one (3a-e) and 4-(5-chloro-2-hydroxyphenyl)-6-(4-substitutedphenyl)-pyrimidin-2-(1H)-thione (4a-e) was achieved through cyclisation of 1-(5-chloro-2-hydroxyphenyl)-3-(4-substitutedphenyl)-prop-2-en-1-one (2a-e) with Urea and thiourea in ethanol containing catalytic amount of KOH respectively. All the synthesized compounds were characterized on the basis of spectral data. These compounds are evaluated for their antimicrobial activity. Some of these compounds show moderate antimicrobial activity as compared to the known reference drugs ciprofloxacin.

**Keywords:** 2-Chlorophenol, aryl aldehyde, urea and thiourea.

## Introduction:

Among a wide variety of heterocycles that have been explored for developing medicinally important molecules, pyrimidine and thiopyrimidines derivatives occupy an important place in the present day therapeutics. Pyrimidines and thiopyrimidines are potential bioactive agents due to their wide spectrum of pharmacological activities<sup>1-5</sup> like anti-inflammatory, antimicrobial, calcium channel blockers, antihypertensive, analgesic, antitumor, antiviral, antibacterial, anti-HIV and anti cancer. Looking to the diversified activities exhibited and in continuation of our work on the synthesis of biologically active heterocycles, we report here in the reaction of different aryl aldehyde with 1-(5-chloro-2-hydroxyphenyl)-ethanone in the presence of NaOH (40%) afforded gives 1-(5-chloro-2-hydroxy phenyl)-3-(4-substitutedphenyl)-prop-2-en-1-one (2a-e). 1-(5-chloro-2-hydroxyphenyl)-3-(4-substitutedphenyl)-prop-2-en-1-one (2a-e) on cyclization with Urea and thiourea in ethanol containing catalytic amount of KOH to afforded 4-(5-chloro-2-hydroxyphenyl)-6-(4-substitutedphenyl)-pyrimidin-2-(1H)-one (3a-e) and 4-(5-chloro-2-hydroxyphenyl)-6-(4-substitutedphenyl)-pyrimidin-2-(1H)-thione (4a-e) respectively.

The structures of the synthesized compounds (3a-e) and (4a-e) have been confirmed by melting point, TLC, IR spectra and NMR spectra.





### Antimicrobial Activity:

All the synthesized compounds were evaluated for their antimicrobial activity by using agar diffusion method<sup>6</sup> against different strains of bacteria such as *S. aureus* and *B. subtilis* a gram positive bacteria and *E. coli* and *S. paratyphi* a gram negative bacteria in nutrient agar medium. Ciprofloxacin was used as reference drugs.

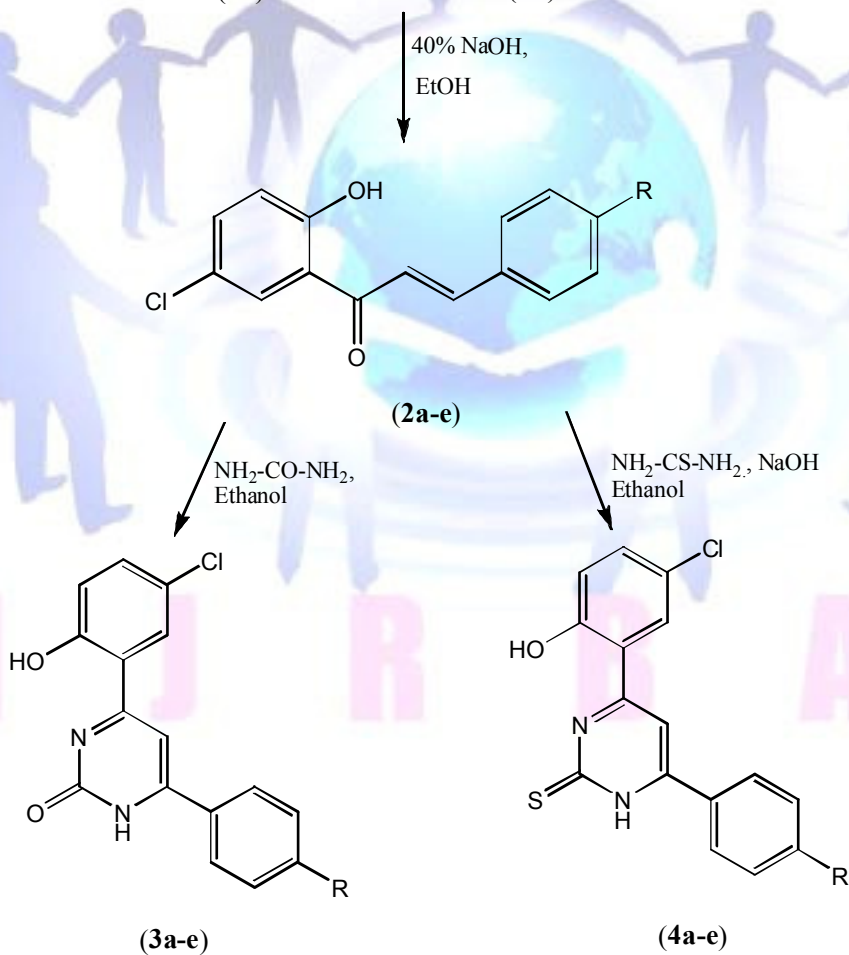
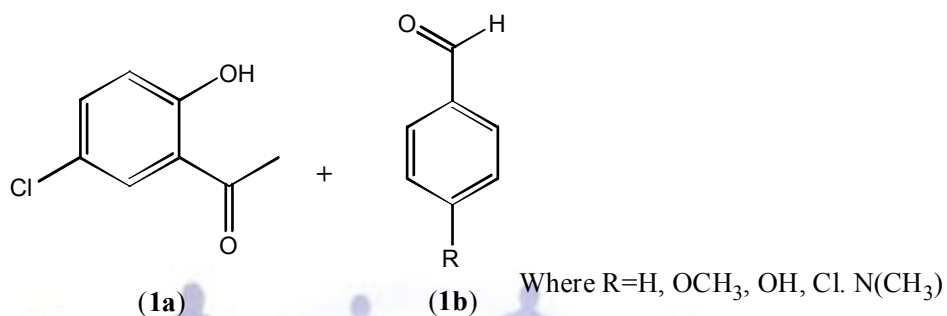
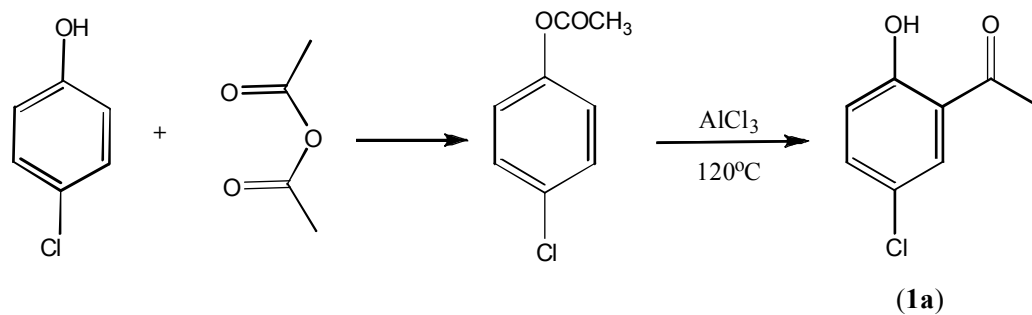
By visualizing Inhibition zone, it could be observed that compounds **3a** and **4c** show excellent antimicrobial activity against the bacterial strain *Staphylococcus aureus*, whereas compounds **3c** and **4d** show moderate activity against *Staphylococcus aureus* as compared to reference drugs. Compound **3a**, **4d** and **4e** were found less active against *B. subtilis*. Whereas remaining compounds were found to be inactive against *B. subtilis*. Compound **3e** and **4c** were found moderate active against *E. coli*. Whereas remaining compounds were found to be inactive against *E. coli*. Compound **3d** found moderate active against *S. paratyphi*. Majority of compounds were found to be inactive against *S. paratyphi*.

### Experimental Section:

**Materials:** 2-Chlorophenol, Anhydrous  $\text{AlCl}_3$ , Acetic anhydride, Benzaldehyde, 4-Methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-hydroxybenzaldehyde, 4-N, N-Dimethylbenzaldehyde, Urea, Thiourea, NaOH, KOH, Ethanol.

All the melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr using Perkin Elmer model 2000 spectrophotometer and reported wave numbers are given in  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  spectra were recorded in  $\text{CDCl}_3$  on a Bruker Advance II 400 MHz spectrophotometer using TMS as an internal standard. Chemical shift values are shown in  $\delta$  ppm. Mass spectra were recorded on Agilent 6320 Ion Trap mass spectrometer. The purity of all the synthesized compounds was checked by TLC on silica gel plates by using appropriate solvents.





SCHEME



### Synthesis of 1-(3-chloro-6-hydroxyphenyl)-ethanone (1a):

4-Chlorophenyl acetate, which is prepared from 4-chlorophenol & acetic anhydride, were mixed with anhydrous  $\text{AlCl}_3$  and heated at  $120\text{ }^\circ\text{C}$  for 45 minutes on oil bath. The reaction mixture was decomposed with ice cold water containing little hydrochloric acid to get crude ketone. It was purified by dissolving in acetic acid and pouring the solution dropwise into cold water with stirring. Yellowish white solid was obtained, m.p.,  $42\text{-}45\text{ }^\circ\text{C}$ , yield, 65 %.

### 1-(5-chloro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (2a):

1-(3-chloro-6-hydroxyphenyl)-ethanone (1a) (0.01 mol) dissolved in ethanol (40 ml) and 4-methoxybenzaldehyde (0.01 mol) was added with constant stirring at room temperature. Then NaOH solution (40%) was added to the reaction mixture with constant stirring, keeping the temperature of the reaction mixture below  $10\text{ }^\circ\text{C}$  throughout the addition. The flask was corked and kept the reaction mixture for 48 hours at room temperature. Finally the reaction mixture was poured over crushed ice and neutralized with glacial acetic acid. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (2a).

**Yield:** 69%, M.P.:  $90\text{-}93\text{ }^\circ\text{C}$ , M.W.: 288.06, Anal. Calculation for  $\text{C}_{16}\text{H}_{13}\text{ClO}_3$ : Found: C: 65.49, H: 5.23, Calcd. C: 66.56, H: 4.54. IR (KBr,  $\text{cm}^{-1}$ ): 1753 (C=O), 1488 (C=C), 1238 (Ar-O), 1200 (C-O).  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz): 3.85 (s, 3H, -OCH<sub>3</sub>), 5.47-5.46 (d, 1H, CO-CH=), 6.93-6.91 (m, 2H, Ar-H), 7.68-6.65 (d 1H, Ar-CH=), 7.91-7.17 (m, 5H, Ar-H). Other compounds of this type (2b-e) were prepared similarly and are recorded in Table-1.

### 4-(5-chloro-2-hydroxyphenyl)-6-(4-methoxyphenyl)-pyrimidin-2(1H)-one (3a).

A mixture of 1-(1-(5-chloro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (2a-e) (0.01 mol) and Urea (0.01 mole) in ethanol (30 ml) containing alcoholic KOH (1mL) were refluxed for 12 hours. Cooled the reaction mixture and poured over crushed ice. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (3a).

**Yield:** 71%, M.P.:  $63\text{-}66\text{ }^\circ\text{C}$ , M.W.: 350.43, Anal. Calculation for  $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}_3$ : Found: C: 62.49, H: 4.21, N: 8.61, Calcd. C: 62.11, H: 3.99, N: 8.52. IR (KBr,  $\text{cm}^{-1}$ ): 3435 (-OH), 3070 (-NH), 2991 (Ar-CH), 1691 (C=O), 1639 (C=N).  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz): 3.83 (s, 3H, -OCH<sub>3</sub>), 5.08 (d, 1H, Ar-H), 6.96-6.94 (s, 2H, Ar-H), 7.26 (s, 1H, -OH), 7.46-7.38 (m, 4H, Ar-H), 7.65-7.63 (d, 1H, Ar-H), 12.87 (s, 1H, -NH). Other compounds of this type (3b-e) were prepared similarly and are recorded in Table-1.

### 4-(5-chloro-2-hydroxyphenyl)-6-(4-methoxyphenyl)-pyrimidin-2(1H)-thione (4a).

A mixture of 1-(1-(5-chloro-2-hydroxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (2a-e) (0.01 mol) and thiourea (0.01 mole) in ethanol (30 ml) containing alcoholic KOH (1mL) were refluxed for 12 hours. Cooled the reaction mixture and poured over crushed ice. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to afford compound (4a).





**Yield:** 67%, M.P.: 180-182 °C, M.W.: 344.82, Anal. Calculation for  $C_{17}H_{13}ClN_2O_2S$ : Found: C: 58.89, H: 3.73, N: 8.02, Calcd. C: 59.21, H: 3.80, N: 8.12. IR (KBr,  $cm^{-1}$ ): 3436 (-OH), 3069 (-NH), 2992 (Ar-CH), 1638 (C=N), 1612 (C=C), 1171 (C-O).  $^1H$  NMR: ( $CDCl_3$ , 400 MHz): 3.87 (s, 3H, -OCH<sub>3</sub>), 6.98-6.94 (m, 3H, Ar-H), 7.26 (s, 1H, -OH), 7.45-7.40 (m, 2H, Ar-H), 7.65-7.63 (d, 2H, Ar-H), 7.85-7.84 (d, 1H, Ar-H), 12.88 (s, 1H, -NH). Other compounds of this type (4b-e) were prepared similarly and are recorded in Table-1.

## Result and Discussion:

The structures of the synthesized compounds were characterized with the help of TLC, IR and NMR. There are no absorptions in the region of 1600-1700  $cm^{-1}$  indicating the absence of -C=N group in 2a compound. The IR spectrum of compounds 3a and 4a shows the characteristic band at 1600-1700  $cm^{-1}$  indicating the presence of C=N group confirmed the cyclisation in pyrimidine and thiopyrimidine derivatives. The  $^1H$  NMR spectrum of compound 2a showed doublet of -CO-CH= at  $\delta$  5.47-5.46 ppm and Ar-CH= at  $\delta$  7.68-7.65 ppm, which confirmed the presence of chalcone moiety. The  $^1H$  NMR spectrum of compound 3a and 4a showed singlet of -NH near about  $\delta$  12.00-13.00 ppm confirmed the cyclisation in pyrimidine and thiopyrimidines derivatives. These compounds are evaluated for their antimicrobial activity. Some of these compounds show moderate antimicrobial activity as compared to the known reference drugs ciprofloxacin.

**Table. 1-** Physicochemical data of the synthesized compounds

Sr. No.	Compds	R	M.P. (°C)	Yield (%)	Molecular Weight	Molecular Formula
1	2a	OCH <sub>3</sub>	90-93	69	288.73	C <sub>16</sub> H <sub>13</sub> ClO <sub>3</sub>
2	2b	H	89-91	62	258.70	C <sub>15</sub> H <sub>11</sub> ClO <sub>2</sub>
3	2c	Cl	165-168	68	293.14	C <sub>15</sub> H <sub>10</sub> Cl <sub>2</sub> O <sub>2</sub>
4	2d	OH	135-138	64	274.70	C <sub>15</sub> H <sub>11</sub> ClO <sub>3</sub>
5	2e	N(CH <sub>3</sub> ) <sub>2</sub>	140-143	59	301.77	C <sub>17</sub> H <sub>16</sub> ClNO <sub>2</sub>
6	3a	OCH <sub>3</sub>	63-66	71	328.75	C <sub>17</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub>
7	3b	H	65-68	65	298.72	C <sub>16</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub>
8	3c	Cl	175-180	67	333.17	C <sub>16</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>
9	3d	OH	120-122	70	314.72	C <sub>16</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub>
10	3e	N(CH <sub>3</sub> ) <sub>2</sub>	140-143	66	341.79	C <sub>18</sub> H <sub>16</sub> ClN <sub>3</sub> O <sub>2</sub>
11	4a	OCH <sub>3</sub>	180-182	67	344.82	C <sub>17</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S
12	4b	H	192-195	71	314.79	C <sub>16</sub> H <sub>11</sub> ClN <sub>2</sub> OS
13	4c	Cl	67-70	59	349.23	C <sub>16</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> OS
14	4d	OH	95-98	63	330.79	C <sub>16</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub> S
15	4e	N(CH <sub>3</sub> ) <sub>2</sub>	240-243	66	357.86	C <sub>18</sub> H <sub>16</sub> ClN <sub>3</sub> OS

## Conclusion:

The present work describes a novel and simple approach for the synthesis of some new 3, 5-disubstituted pyrimidine and thiopyrimidine derivatives. The structures of the synthesized compounds were characterized with the help of TLC, IR and NMR.





## Acknowledgment:

The authors are grateful to the authorities of JanataMahavidyalaya, Chandrapur and ShriShivaji Science College, Amravati for providing necessary facilities. RSIC, Chandigarh for spectral analyses.

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