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# Synthesis and Antimicrobial Activity of Tri-Substituted 1,6-Dihydropyrimidines

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A series of substituted 1,6-dihydropyrimidines compounds have been synthesized by the reaction of ethylcyanoacetate, thiourea and substituted aldehydes in the presence of potassium carbonate and ethanol. Reactions have been carried out by conventional and microwave methods. The synthesized compounds are screened for their antibacterial and antifungal activity against *Staphylococcus aureus, Escherichia coli* and *Candida albicans, Aspergillus flavus*, respectively.

**Key Words: Synthesis, 1,6-Dihydropyrimidines, Microwave, Antibacterial activity.**

## INTRODUCTION

Heterocyclic synthesis as emerged as powerful technique for generating new molecules useful for drug discovery[1]. Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs[2]. Heterocyclic compounds containing two nitrogen atoms in the molecule represent a important group of organic compounds because many of them exhibit significant biological activity[3]. Pyrimidines have been the subject of substantial attention by synthetic and medicinal chemists because of the role of this heteroaromatic ring in many biological systems.

Pyrimidines, being an integral part of DNA and RNA imparts diverse pharmacological properties as effective bactericide and fungicides[4-6]. Certain pyrimidine derivatives are also known to display antimalarial, antifilarial, antileishmanial and anti-HIV activities[7-10]. Even some of the 3-4, dihydropyrimidines (DHPM) have emerged as integral backbones of several calcium channel blockers, antihypertensive agents, adrenergic and neuropeptide antagonist[11].

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Several alkaloids containing 3,4-dihydropyrimidines have been isolated from marine sources and among them are the batzelladine alkaloids which are to be potent HIV-gp-120-CD4 inhibitors[12,13].

Application of microwave irradiation is used for carrying out chemical transformations which are pollution free and eco friendly[14,15]. Commercial microwave oven is used as convenient source of heat in laboratory. The microwave assisted organic reactions occur more rapidly and safely a higher chemical yields[16,17], render the microwave method superior to conventional method.

Ethylcyanoacetate on condensation with thiourea and substituted aryl aldehydes in presence of potassium carbonate in absolute alcohol gives 4-(substituted)-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidines[18,19].

## EXPERIMENTAL

All melting points were uncorrected and measured using an Electrothermal IA 9100 apparatus (Shimadzu, Japan). The purity of compounds was checked by TLC on silica gel G coated glass plates (Merck, Damstadt, Germany). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer KBr on Unicam FTIR and Perkin-Elmer FT-IR Spectrum 1000 Spectrophotometers (Shimadzu, Japan). The NMR spectra were recorded on Jeol Model AMX 400 FT NMR Spectrophotometer using DMSO-$d_6$ as solvent and TMS as internal standard reference. Chemical shifts are expressed as δ values (ppm). Microwave reactions were carried out in a LG MS-192w domestic microwave oven (LG Electronics, Japan).

### 4-(*p*-Methoxy)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4a)

**Conventional method:** A mixture of ethylcyanoacetate **2** (5.7g. 50 mmol) thiourea **3** (3.8 g, 50 mmol), anisaldehyde **1** (2.74 g, 50 mmol), potassium carbonate (6.9 g, 50 mmol) in absolute ethanol (50 mL) was refluxed for 12 h and the mixture was neutralized with glacial acetic acid. The product was filtered and crystallized from aqueous ethanol.

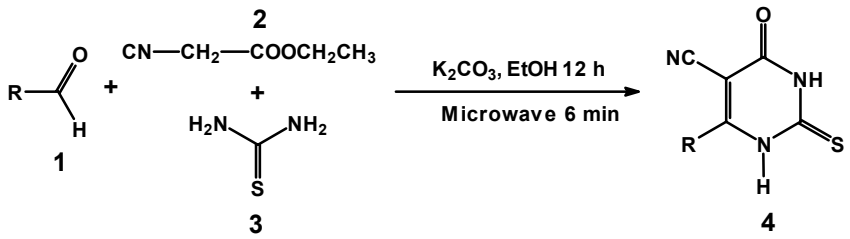
**Microwave method:** Required quantity of reactants as mentioned above are taken and about 20 mL of alcohol in a conical flask, subjected for microwave irradiation for three intermittent cycles of duration 2 min at 160 watts. Then neutralized with glacial acetic acid. The obtained product was filtered and crystallized by aqueous ethanol.

By the same procedure, compounds **4b-j** were prepared. Their characterization data are recorded in Table-1.

**Antimicrobial activity:** Synthesized compounds were screened for antibacterial and antifungal activities at two different conc. (50 μg/mL, 100 μg/mL,) against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*, *Aspergillus flavus* by cup plate method[20] using procaine penicillin, streptomycin and griseofulvin as standards, respectively.

## RESULTS AND DISCUSSION

Synthetic pathway is presented in **Scheme-I** and physico-chemical data for the synthesized compounds are given in Table-1. The antimicrobial activities are depicted in Tables 2 and 3. The conventional method reaction took 12 h, whereas the synthesis by microwave irradiation took only 6 min.




R = (a) 4-$OCH_3$-$C_6H_4$; (b) 2-F-$C_6H_4$; (c) 2-Furyl;
(d) 2-Thienyl; (e) 4-N-$(CH_3)_2$-$C_6H_4$; (f) 4-Cl-$C_6H_4$;
(g) 2-Cl-$C_6H_4$; (h) 2,3-$(OCH_3)_2$-$C_6H_3$; (i) 2-OH-$C_6H_3$;
(j) 2,3$(OH)_2$-$C_6H_3$

**Scheme-I**

TABLE-1
CHARACTERIZATION DATA OF COMPOUNDS **4a-j**

| Compd. | Yield (%) Conv.† | Yield (%) M.I.‡ | m.p. (ºC) | m.f. | m.w. | $R_f$ value* | RC Sol. |
|---|---|---|---|---|---|---|---|
| **4a** | 60 | 69 | 273 | $C_{12}H_9N_3O_2S$ | 259.2 | 0.45 | EtOH |
| **4b** | 65 | 78 | 240 | $C_{11}H_6N_3OSF$ | 247.2 | 0.53 | EtOH |
| **4c** | 67 | 79 | 152 | $C_9H_5N_3O_2S$ | 219.2 | 0.56 | EtOH |
| **4d** | 70 | 85 | 154 | $C_9H_5N_3OS_2$ | 235.2 | 0.43 | EtOH |
| **4e** | 73 | 87 | 272 | $C_{13}H_{12}N_4OS$ | 272.3 | 0.62 | DMF |
| **4f** | 74 | 81 | 260 | $C_{11}H_6N_3OSCl$ | 263.7 | 0.47 | EtOH |
| **4g** | 51 | 69 | 249 | $C_{11}H_6N_3OSCl$ | 263.7 | 0.56 | EtOH |
| **4h** | 56 | 67 | 200 | $C_{13}H_{11}N_3O_3S$ | 289.3 | 0.49 | EtOH |
| **4i** | 67 | 86 | 270 | $C_{11}H_7N_3O_2S$ | 245.2 | 0.54 | EtOH |
| **4j** | 58 | 79 | 245 | $C_{11}H_7N_3O_3S$ | 261.2 | 0.65 | DMF |

†Conv. = Conventional; ‡M.I. = Microwave irradiation
*Solvent system ethyl acetate:butanol:chloroform 1:2:1

**4-(*p*-Methoxy)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4a):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 2200 (CN *str.*), 1680 (CO of pyrimidine), 1520 (C=N *str.*), 1500 (aromatic C=C), 1248 (C=S *str.*), 1215 (C-O-C *str.*); $^1H$ NMR: δ 3.8 (3H, s, -$OCH_3$), 7.1-7.8 (4H, d, -Ar-H), 13.2 (1H, s, -NH).

TABLE-2
ANTIBACTERIAL ACTIVITY OF COMPOUNDS **4a-j**

| Compound | Zone of inhibition after 24 h (mm) | | | |
|---|---|---|---|---|
| | *Escherichia coli* | | *Staphylococcus aureus* | |
| | 50 mcg | 100 mcg | 50 mcg | 100 mcg |
| **4a** | 08 | 15 | 9 | 16 |
| **4b** | 15 | 18 | 16 | 25 |
| **4c** | 14 | 19 | 14 | 21 |
| **4d** | 09 | 14 | 9 | 17 |
| **4e** | 11 | 14 | 10 | 18 |
| **4f** | 15 | 16 | 11 | 20 |
| **4g** | 14 | 17 | 9 | 16 |
| **4h** | 14 | 16 | 11 | 20 |
| **4i** | 15 | 15 | 8 | 15 |
| **4j** | 13 | 15 | 8 | 16 |
| Penicillin | 19 | 28 | – | – |
| Streptomycin | – | – | 20 | 31 |

TABLE-3
ANTIFUNGAL ACTIVITY OF COMPOUNDS **4a-j**

| Compound | Zone of inhibition after 24 h (mm) | | | |
|---|---|---|---|---|
| | *Aspergillus flavus* | | *Candida albicans* | |
| | 50 mcg | 100 mcg | 50 mcg | 100 mcg |
| **4a** | 14 | 21 | 15 | 22 |
| **4b** | 16 | 19 | 12 | 20 |
| **4c** | 10 | 17 | 11 | 17 |
| **4d** | 13 | 19 | 16 | 17 |
| **4e** | 09 | 15 | 14 | 18 |
| **4f** | 11 | 16 | 15 | 14 |
| **4g** | 14 | 18 | 13 | 19 |
| **4h** | 11 | 16 | 14 | 17 |
| **4i** | 13 | 17 | 13 | 17 |
| **4j** | 12 | 18 | 15 | 18 |
| Griseofulvin | 15 | 23 | – | – |
| Nystatin | – | – | 17 | 26 |

**4-(*o*-Fluoro)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4b):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 2220 (CN *str.*), 1670 (CO of pyrimidine), 1530 (C=N *str.*), 1510 (aromatic C=C), 1240 (C=S *str.*), 1010 (C-F *str.*) ; $^1$H NMR: δ 7.2-7.5 (4H, m, Ar-H), 13.2 (1H, s, -NH).

**4-(2'-Furyl)-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4c):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 2215 (CN *str.*), 1660 (CO of pyrimidine), 1525 (C=N *str.*), 1525 (aromatic C=C), 1250 (C=S *str.*), 1235 (C-O-C *str.*); $^1$H NMR: δ 7.3-7.6-8.0 (3H q-d-d, Ar-H) 11.4 (1H, s,-NH).

**4-(2'-Thienyl)-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4d):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 2220 (CN *str.*), 1670 (CO of pyrimidine), 1520 (C=N *str.*), 1520 (aromatic C=C), 1260 (C=S *str.*); $^1$H NMR: δ 7.2-7.8-8.1 (3H q-d-d, Ar-H) 11.5 (1H, s, -NH ).

**4-(4'-Dimethylamine)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4e):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 2220 (CN *str.*), 1650 (CO of pyrimidine), 1620 (C=N *str.*), 1570 (aromatic C=C), 1340 (N-$(CH_3)_2$ *str.*), 1270 (C=S *str.*); $^1$H NMR: δ 3.0 (6H, s, -N$(CH_3)_2$, 8.0-7.6 (4H, d, Ar-H), 12.2 (1H, s, -NH).

**4-(4'-Chloro)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4f):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 2225 (CN *str.*), 1640 (CO of pyrimidine), 1600 (C=N *str.*), 1560 (aromatic C=C ), 1250 (C=S *str.*) 760 (C-Cl str.); $^1$H NMR: δ 7.2-7.6 (4H, d, -Ar-H), 13.0 (1H, s, -NH).

**4-(2'-Chloro)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4g):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 2215 (CN *str.*), 1670 (CO of pyrimidine), 1580 (C=N *str.*), 1550 (aromatic C=C ), 1240 (C=S *str.*) 770 (C-Cl stretching); $^1$H NMR: δ 7.0-7.4 (4H, m, -Ar-H), 13.2 (1H, s, -NH).

**4-(2',3'-Dimethoxy)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4h):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 2225 (CN *str.*), 1700 (CO of pyrimidine), 1610 (C=N *str.*), 1500 (aromatic C=C), 1260 (C=S *str.*) 1215 (C-O-C *str.*); $^1$H NMR: δ 3.7 (6H, s, -$OCH_3$), 6.6-6.7 (3H, m, Ar-H) 8.2 (1H, s, -NH).

**4-(2'-Hydroxy)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4i):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3400 (OH *str.*), 2210 (CN *str.*), 1700 (CO of pyrimidine), 1610 (C=N *str.*), 1500 (aromatic C=C), 1260 (C=S *str.*); $^1$H NMR: δ 4.5 (1H, s, -OH), 7.2-7.5 (4H, m, Ar-H), 13.2 (1H, s, -NH).

**4-(2',3'-Dihydroxy)phenyl-2-mercapto-5-cyano-6-oxo-1,6-dihydropyrimidine (4j):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3450 (OH *str.*), 2220 (CN *str.*), 1710 (CO of pyrimidine), 1620 (C=N *str.*), 1510 (aromatic C=C), 1270 (C=S *str.*); $^1$H NMR: δ 5.0 (2H, s, -OH), 6.1-6.8 (3H, m, Ar-H), 8.2 (1H, s, -NH)

**Antimicrobial activity:** The compounds **4b**, **4c**, **4d** and **4f** showed promising activity against *E. coli* and *S. aureus* and considerable activity against *Candida albicans* and *Aspergillus flavus*. Other compounds showed moderate activity (Tables 2 and 3).

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