# Synthesis of Some New Dihydropyrimidines by Iodine as a Catalyst at Ambient Temperature and Evaluation of Their Biological Activity

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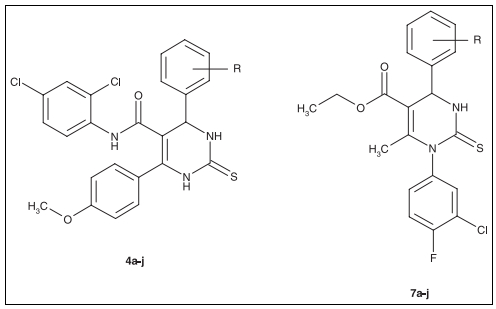


An improved method for the synthesis of some new dihydropyrimidines from aromatic aldehydes, 1,3-dicarbonyl compounds, and thiourea with significant enhancement in reaction rates, short reaction time (4–6 h), good to excellent yields (70–93%), and ambient temperature using molecular iodine as catalyst is described. The biological evaluation revealed that the newly synthesized compounds **4a–j** and **7a–j** exhibited good antimicrobial activity and moderate antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}RV$.

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## INTRODUCTION

3,4-Dihydropyrimidinones denoted as Biginelli compounds, and their derivatives are highly important heterocyclic units in the realm of natural and synthetic organic chemistry that possess diverse therapeutic and pharmacological properties [1],[2] so the synthesis of these compounds has become an important target in current years. The diversity, efficiency, and rapid access to small and highly functionalized organic molecules makes this approach of central current interest in the construction of compounds library and optimization in drug discovery process [3].

The dihydropyrimidine (DHPM) nucleus exhibits a broad spectrum of biological effects such as antitumor [4], antibacterial [5], anti-inflammatory [2], and anti-viral [2],[5],[6] activities. Furthermore, appropriately functionalized DHPMs have emerged as calcium channel blockers, antihypertensive, $\alpha 1_a$-adrenrgic antagonists, and neuropeptide Y 7 antagonists, antimitotic [7], anticarcinogenic [8], and antihypertensive [9] agents, and additionally, their particular structure has been found in natural marine alkaloid batzelladine which are the first low molecular weight natural products reported in the literature to inhibit the binding of HIV gp-120 to CD4 cells, so disclosing a new field toward the development of AIDS therapy [10].

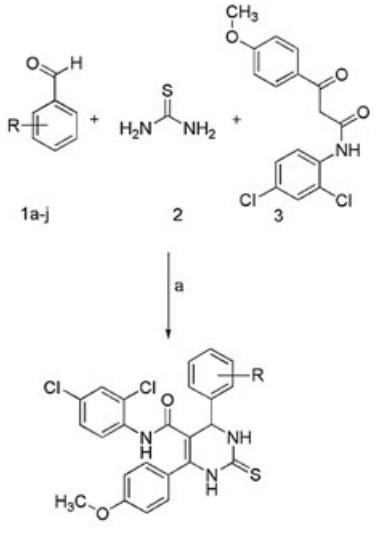
Molecular iodine [11] has attracted attention as an inexpensive, readily available catalyst for various organic transformations to afford the corresponding products in excellent yield with high selectivity. There are only few reports about its use for the synthesis of DHPMs [12] and 1,4-DHPs [13].

In continuation of our work on the development of useful synthetic methodologies by using molecular iodine catalysts [14], we observed that molecular iodine is an efficient catalyst for the synthesis of DHPMs via Biginelli condensation. Herein, we report the synthesis, antimycobacterial and antimicrobial activity of some new 3,4-dihydropyrimidin-2(1H)-ones.

## RESULTS AND DISCUSSION

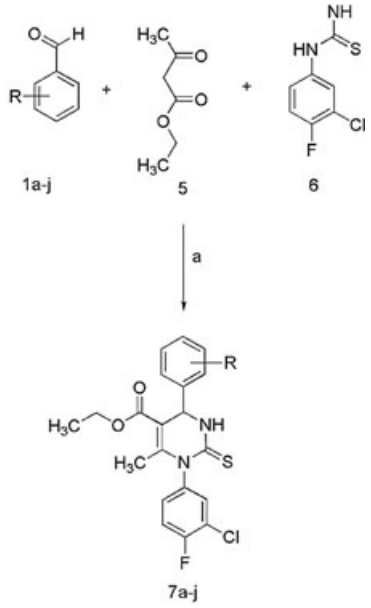
The synthesis of 3,4-dihydropyrimidin-2(1H)-ones **4a–j** and **7a–j** were performed in the following steps shown in reaction (Scheme 1) and (Scheme 2). The required intermediates **3** [15] and **6** [16] have been prepared by the literature methods (Scheme 3). The compounds **4a–j** were synthesized by The one-pot three-components condensation reaction of substituted arylaldehydes **1a–j** with thiourea **2** and *N*-(2,4-dichlorophenyl)-3-4-methoxyphenyl)-3-oxopropanamide **3** proceeded smoothly in ethanol in the presence of 5 mol % iodine [12] as a catalyst. Compounds **7a–j** was synthesized by the use of substituted arylaldehydes **1a–j**, *N*-(3-chloro-4-fluorophenyl) thiourea **6**

**Scheme 1**




**Reagents and conditions:** (a) 5 mol% Iodine, ethanol, rt

**Scheme 2**

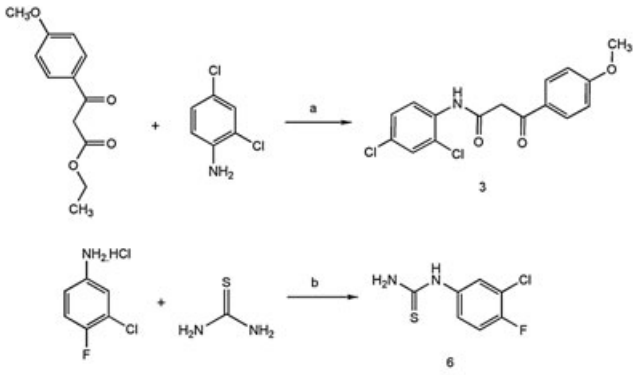



**Reagents and conditions:** (a) 5 mol% Iodine, ethanol, rt

and ethyl acetoacetate **5** as per same procedure, to give the excellent yields. Synthesis of compounds **4a–j** and **7a–j** was carried out by the use of acid catalyst to give poor yield and longer reaction time as compare with iodine catalyst, shown in (Table 1).

A possible role of the molecular iodine in the formation of DHPMs as described in the literature, iodine may catalyze the reaction as a mild Lewis acid [5],[17]. The

**Scheme 3**




**Reagents and conditions:** (a) NaOH, toluene, 110 °C; (b) HCl, gl.$CH_3COOH$, 150 °C.

purity of all the synthesized compounds was checked by thin layer chromatography (TLC). The structures of the synthesized compounds were assigned on the basis of spectral data like IR, $^1$H-NMR, mass spectral analysis, and elemental analysis. All the newly synthesized compounds were in full agreement with the proposed structures.

**Antimycobacterial activity.** All the newly synthesized compounds were evaluated for their possible *in vitro* antimycobacterial activity under the Tuberculosis Antimicrobial Acquisition Coordinating Facility, an anti-tuberculosis drug discovery program, coordinated by the Southern Research Institute (Birmingham, AL) directed by the National Institute of Allergy and Infectious Diseases, U.S.A. Initially, compounds **4a–j** and **7a–j** were evaluated against *Mycobacterium tuberculosis* $H_{37}$RV [American type culture collection (ATCC) 27294] (American Type Culture Collection, Manassas, VA) at single concentration of 6.25 μg/mL in BACTEC 12B medium using both micro dilution assay and the micro plate Alamar blue assay [18]. Compounds exhibiting fluorescence were tested in the BACTEC 460 radiometric system [19] The antitubercular activity data were compared with standard drug rifampin at 0.25 μg/mL concentrations, which showed 98% inhibition (Table 2). The structure–activity relationship studies revealed that compounds containing 4-substituted phenyl at 4- and 4,2-position of DHPMs were most active as compared with 2- and 3-substituted phenyl ring derivatives. Although compounds **7a–j** are the weakest in activity as compared with compounds **4a–j** of these derivatives, compound **4d** (—**3-OCH$_3$**), **4f** (—**4-F**), **4h** (—**2-OH**, **4-OCH$_3$**) of DHPMs was the most active as compared with other compounds. However, all the new derivatives showed weak antimycobacterial activity compared with the standard drug rifampin, which exhibited 98% growth inhibition at 6.25 lg/mL concentrations (Table 2).

**Table 1**

Synthesis of **4a–j** and **7a–j** using iodine and acid catalyst.

| | | | Iodine catalyst | | Acid catalyst (HCl) | |
|---|---|---|---|---|---|---|
| Sr. No. | Entry | R | Time (h) | Yield (%) | Time (h) | Yield (%) |
| 1 | **4a** | H | 4.4 | 83 | 12.3 | 63 |
| 2 | **4b** | 2-$NO_2$ | 4.3 | 87 | 15.0 | 57 |
| 3 | **4c** | 3-$NO_2$ | 5.0 | 78 | 17.0 | 61 |
| 4 | **4d** | 3-$OCH_3$ | 5.4 | 73 | 18.3 | 66 |
| 5 | **4e** | 4-$OCH_3$ | 7.0 | 84 | 13.3 | 45 |
| 6 | **4f** | 4-F | 5.2 | 93 | 15.3 | 75 |
| 7 | **4g** | 2-Cl | 5.5 | 88 | 16.0 | 67 |
| 8 | **4h** | 2-OH,4-$OCH_3$ | 6.0 | 79 | 14.0 | 59 |
| 9 | **4i** | 4-$N(CH_3)_2$ | 5.2 | 74 | 15.3 | 62 |
| 10 | **4j** | $C_{10}H_7$ | 6.1 | 75 | 13.0 | 53 |
| 11 | **7a** | H | 4.5 | 87 | 18.0 | 71 |
| 12 | **7b** | 2-$NO_2$ | 5.3 | 81 | 12.0 | 64 |
| 13 | **7c** | 3-$NO_2$ | 6.0 | 73 | 15.0 | 49 |
| 14 | **7d** | 3-$OCH_3$ | 6.3 | 90 | 18.3 | 54 |
| 15 | **7e** | 4-$OCH_3$ | 7.0 | 77 | 16.3 | 66 |
| 16 | **7f** | 4-F | 4.5 | 89 | 15.0 | 70 |
| 17 | **7g** | 2-Cl | 5.0 | 82 | 17.0 | 55 |
| 18 | **7h** | 2-OH,4-$OCH_3$ | 6.3 | 85 | 12.0 | 47 |
| 19 | **7i** | 4-$N(CH_3)_2$ | 5.5 | 76 | 16.0 | 58 |
| 20 | **7j** | $C_{10}H_7$ | 6.1 | 78 | 13.0 | 60 |

**Table 2**

Antimicrobial screening results of compounds **4a–j** and **7a–j.**

| | | Zones of inhibition (mm) | | | | |
|---|---|---|---|---|---|---|
| | | Antimicrobial activity | | | | Antifungal activity |
| Entry | % Inhibition antitubercular activity | *B. megaterium* | *P. aeruginosa* | *E. coli* | *S. aureus* | *A. niger* |
| **4a** | 45 | 11 | 15 | 20 | 17 | 12 |
| **4b** | 00 | 17 | 12 | 14 | 10 | 13 |
| **4c** | 33 | 00 | 13 | 15 | 12 | 15 |
| **4d** | 51 | 21 | 18 | 19 | 17 | 11 |
| **4e** | 41 | 11 | 11 | 13 | 11 | 12 |
| **4f** | 49 | 20 | 18 | 17 | 16 | 21 |
| **4g** | 05 | 18 | 17 | 17 | 14 | 23 |
| **4h** | 52 | 19 | 16 | 10 | 17 | 17 |
| **4i** | 34 | 15 | 18 | 12 | 14 | 16 |
| **4j** | 24 | 12 | 13 | 18 | 11 | 17 |
| **7a** | 40 | 14 | 10 | 18 | 18 | 18 |
| **7b** | 10 | 13 | 18 | 15 | 17 | 18 |
| **7c** | 37 | 11 | 14 | 13 | 16 | 17 |
| **7d** | 33 | 20 | 16 | 13 | 17 | 17 |
| **7e** | 48 | 18 | 18 | 17 | 19 | 19 |
| **7f** | 43 | 14 | 11 | 14 | 15 | 13 |
| **7g** | 06 | 12 | 12 | 11 | 12 | 15 |
| **7h** | 47 | 15 | 18 | 20 | 11 | 16 |
| **7i** | 00 | 17 | 20 | 15 | 13 | 15 |
| **7j** | 00 | 10 | 13 | 14 | 18 | 14 |
| Amoxicillin | – | 21 | 24 | 25 | 25 | 00 |
| Benzyl–Penicillin | – | 20 | 18 | 18 | 15 | 00 |
| Ampicillin | – | 20 | 24 | 22 | 21 | 00 |
| Norfloxacin | – | 18 | 17 | 24 | 25 | 00 |
| Greseofulvin | – | 00 | 00 | 00 | 00 | 24 |

**Antimicrobial activity.** The antimicrobial activity was assayed by using the cup-plate agar diffusion method [20] by measuring the zone of inhibition in mm. Newly synthesized compounds were screened *in vitro* for their antimicrobial activity against varieties of bacterial strains such *Bacillus megaterium* ATCC 14518, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, and fungi *Aspergillus niger* ATCC 9029 at 40 μg/mL concentration. Standard drugs like ampicillin, amoxicillin, norfloxacin, benzyl penicillin, and greseofulvin were used for the comparison purpose. The results are given in Table 2.

From the result of antimicrobial data, compounds **4d**, **4g**, **4h**, **7d**, and **7e** were active and compounds **7b**, **7i**, **7h**, and **7i** were moderately active against *B. megaterium*. Same as compounds **4d**, **4f**, **4i**, **7b**, **7e**, **7h**, and **7i** were active, whereas compounds **4a**, **4g**, **4h**, **7c**, and **7d** were moderately active against *P. aeruginosa*. Further compounds **4a**, **4d**, **4j**, **7a**, and **7h** were active and compounds **4c**, **4f**, **4g**, **7b**, and **7i** show moderate activity against *E. coli*. In case of S. *aureus*, compounds **4a**, **7e**, and **7j** were active and compounds **4d**, **4f**, **4h**, **7b**, and **7c** were moderately active. Against *A. niger* compounds **4d**, **4f**, **4g**, **7a**, **7b**, and **7e** were active, whereas compounds **4h**, **4i**, **4j**, **7c**, **7d**, and **7h** moderately active. Remaining compounds did not show any promising activity against tested bacteria and fungi.

## EXPERIMENTAL

Melting points were determined on electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 $F_{254}$ (Merck, St. Louis, MO). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan), using DRS prob. $^1$H-NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer (Bruker, Rheinstetten, Germany), in $CDCl_3$. Chemical shifts are expressed in δ ppm downfield from Tetra methyl silane (TMS) as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan). Elemental analysis was performed on a Carlo-Erba EA 1108 elemental analyzer (Waltham, MA). Solvents were evaporated with a Laborota 4000 efficient rotary evaporator (Heidolph, Germany).

**Preparation of *N*-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide (3).** A mixture of ethyl-3-(4-methoxyphenyl) -3-oxopropanoate (2.22 g, 10 mmol) and 2,4-dichloro aniline (1.62 g, 10 mmol) in ethanol was refluxed for 10 h. The resulting solution was poured over crushed ice. The separated solid was filtered and crystallized from ethanol, Yield 71%, mp 267°C.

**Preparation of *N*-(3-chloro-4-fluorophenyl) thiourea (6).** To a mixture of 3-chloro-4-fluoroaniline hydrochloride (18.1 g, 100 mmol) and thiourea (24.0 g, 400 mmol) in water (40 mL), concentrated HCl (1 mL) and glacial acetic acid (1 mL) were added. The content was refluxed for 12 h. After completion of the reaction, content was poured in to ice water. Excess of hydrochloric acid was removed with hot water, and crude product was isolated and crystallized from methanol. Yield 89%, mp 236°C.

**General procedure for the preparation of *N*-(2,4-dichlorophenyl)-1,2,3,4-tetrahydro-6-(4-methoxyphenyl)-4-aryl-2-thioxopyrimidine-5-carboxamides (4a–j).** A mixture of thiourea **2** (0.76 g, 10 mmol), *N*-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide **3** (3.38 g, 10 mmol), different substituted aryl aldehydes **1a–j** (10 mmol) and iodine (5 mol%) in ethanol (15 mL) was stirred at room temperature until the reaction was completed (4–6 h monitored by TLC). The reaction mixture was treated with 0.1*N* $Na_2S_2O_3$ solution and extracted into ethyl acetate. The solvent was removed *in vacuo*, and the resulting crude product was crystallized from ethanol to give the analytical pure compounds **4a–j**.

***N*-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydro-6-(4-methoxyphenyl)-4-phenyl-2-thioxopyrimidine-5-carboxamide (4a).** Yield 83%; mp 257–259°C; IR (KBr): 3432, 3064, 2923, 1683, 1542, 1452, 1406, 765 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.17 (s, 1H, NH), 9.95 (s, 1H, NH), 8.87 (s, 1H, NH), 7.56 (d, 2H, Ar—H), 7.37–7.25 (m, 8H, Ar—H), 6.97 (d, 2H, Ar—H), 5.56 (s, 1H, CH), 3.91 (s, 3H, $OCH_3$); MS: *m/z* = 484 [$M^+$]; Anal. Calcd. for $C_{24}H_{19}Cl_2N_3O_2S$: C, 59.51; H, 3.95; N, 8.67%. Found: C, 59.54; H, 3.96; N, 8.66%.

***N*-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydro-6-(4-methoxyphenyl)-4-(2-nitrophenyl)-2-thioxopyrimidine-5-carboxamide (4b).** Yield 87%; mp 209–211°C; IR (KBr): 3425, 3079, 2917, 1716, 1682, 1573, 1466, 746 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H, NH), 9.79 (s, 1H, NH), 8.73 (s, 1H, NH), 7.61 (d, 2H, Ar−H), 7.47–7.39 (m, 7H, Ar−H), 6.91 (d, 2H, Ar−H), 5.42 (s, 1H, CH), 3.81 (s, 3H, $OCH_3$); MS: *m/z* = 529 [$M^+$]; Anal. Calcd. for $C_{24}H_{18}Cl_2N_4O_4S$: C, 54.45; H, 3.43; N, 10.58%. Found: C, 54.47; H, 3.41; N, 10.57%.

***N*-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydro-6-(4-methoxyphenyl)-4-(3-nitrophenyl)-2-thioxopyrimidine-5-carboxamide (4c).** Yield 78%; mp 226–228°C; IR (KBr): 3453, 3082, 2956, 1698, 1620, 1543, 1421, 720 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.21 (s, 1H, NH), 9.91 (s, 1H, NH), 8.81 (s, 1H, NH), 7.67 (d, 2H, Ar−H), 7.43–7.28 (m, 7H, Ar−H), 6.83 (d, 2H, Ar−H), 5.63 (s, 1H, CH), 3.88 (s, 3H, $OCH_3$); MS: *m/z* = 529 [$M^+$]; Anal. Calcd. for $C_{24}H_{18}Cl_2N_4O_4S$: C, 54.45; H, 3.43; N, 10.58%. Found: C, 54.49; H, 3.42; N, 10.56%.

***N*-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydro-4-(3-methoxyphenyl)-6-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (4d).** Yield 73%; mp 222–224°C; IR (KBr): 3478, 3073, 2968, 1714, 1628, 1530, 1481, 768 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H, NH), 9.54 (s, 1H, NH), 8.59 (s, 1H, NH), 7.54 (d, 2H, Ar−H), 7.47–7.34 (m, 7H, Ar−H), 6.87 (d, 2H, Ar—H), 5.37 (s, 1H, CH), 3.73 (s, 6H, $OCH_3$); MS: *m/z* = 514 [$M^+$]; Anal. Calcd. for $C_{25}H_{21}Cl_2N_3O_3S$: C, 58.37; H, 4.11; N, 8.17%. Found: C, 58.29; H, 4.13; N, 8.19%.

***N*-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydro-4,6-bis-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (4e).** Yield 84%; mp 286–288°C; IR (KBr): 3439, 3019, 2945, 1725, 1640, 1509, 1451, 742 cm$^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H, NH), 9.76 (s, 1H, NH), 8.63 (s, 1H, NH), 7.63 (d, 2H, Ar−H), 7.49–7.38 (m, 7H, Ar−H), 6.74 (d, 2H, Ar−H), 5.48 (s, 1H, CH), 3.91 (s, 6H, $OCH_3$); MS: *m/z* = 514 [$M^+$]; Anal. Calcd. for $C_{25}H_{21}Cl_2N_3O_3S$: C, 58.37; H, 4.11; N, 8.17%. Found: C, 58.32; H, 4.12; N, 8.17%.

***N-(2,4-Dichlorophenyl)-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (4f).*** Yield 93%; mp 285–287°C; IR (KBr): 3410, 3092, 2958, 1736, 1642, 1530, 1418, 756 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H, NH), 9.98 (s, 1H, NH), 8.91 (s, 1H, NH), 7.65 (d, 2H, Ar−H), 7.55–7.40 (m, 7H, Ar−H), 6.73 (d, 2H, Ar−H), 5.66 (s, 1H, CH), 3.79 (s, 3H, $OCH_3$); MS: *m/z* = 502 [$M^+$]; Anal. Calcd. for $C_{24}H_{18}Cl_2FN_3O_2S$: C, 57.38; H, 3.61; N, 8.36%. Found: C, 57.39; H, 3.67; N, 8.33%.

***N-(2,4-Dichlorophenyl)-4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (4g).*** Yield 88%; mp 153–155°C; IR (KBr): 3435, 3087, 2936, 1700, 1665, 1550, 1425, 720 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H, NH), 9.73 (s, 1H, NH), 8.54 (s, 1H, NH), 7.58 (d, 2H, Ar−H), 7.43–7.30 (m, 7H, Ar−H), 6.94 (d, 2H, Ar−H), 5.47 (s, 1H, CH), 3.83 (s, 3H, $OCH_3$); MS: *m/z* = 519 [$M^+$]; Anal. Calcd. for $C_{24}H_{18}Cl_3N_3O_2S$: C, 55.56; H, 3.50; N, 8.10%. Found: C, 55.60; H, 3.53; N, 8.08%.

***N-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydro-4-(2-hydroxy-4-methoxyphenyl)-6-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (4h).*** Yield 79%; mp 326–328°C; IR (KBr): 3422, 3047, 2923, 1719, 1644, 1549, 1462, 748 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H, NH), 9.81 (s, 1H, NH), 8.85 (s, 1H, NH), 7.39 (d, 2H, Ar−H), 7.23–7.18 (m, 6H, Ar), 6.79 (d, 2H, Ar−H), 5.44 (s, 1H, CH), 4.91 (s,1H, OH), 3.76 (s, 6H, $OCH_3$); MS: *m/z* = 530 [$M^+$]; Anal. Calcd. for $C_{25}H_{21}Cl_2N_3O_4S$: C, 56.61; H, 3.99; N, 7.92%. Found: C, 56.67; H, 3.91; N, 7.90%.

***N-(2,4-Dichlorophenyl)-4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (4i).*** Yield 74%; mp 222–224°C; IR (KBr): 3392, 3117, 2933, 1693, 1666, 1522, 1442, 773 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H, NH), 9.37 (s, 1H, NH), 8.48 (s, 1H, NH), 7.59 (d, 2H, Ar−H), 7.17–7.08 (m, 7H, Ar−H), 6.93 (d, 2H, Ar−H), 5.51 (s, 1H, CH), 3.86 (s, 3H, OH), 2.81 (s, 6H, $OCH_3$); MS: *m/z* = 527 [$M^+$]; Anal. Calcd. for $C_{26}H_{24}Cl_2N_4O_2S$: C, 59.26; H, 4.63; N, 10.60%. Found: C, 59.21; H, 4.67; N, 10.53%.

***N-(2,4-Dichlorophenyl)-1,2,3,4-tetrahydro-6-(4-methoxyphenyl)-4-(naphthalen-1-yl)-2-thioxopyrimidine-5-carboxamide (4j).*** Yield 75%; mp 305–307°C; IR (KBr): 3419, 3062, 2925, 1706, 1676, 1566, 1471, 736 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H, NH), 9.78 (s, 1H, NH), 8.68 (s, 1H, NH), 7.59–7.19 (m, 10H, Ar−H), 7.14 (d, 2H, Ar−H), 6.77 (s, 2H, CH), 5.31 (s, 1H, OH), 3.71 (s, 3H, $OCH_3$); MS: *m/z* = 534 [$M^+$]; Anal. Calcd. for $C_{28}H_{21}Cl_2N_3O_2S$: C, 62.92; H, 3.96; N, 7.86%. Found: C, 62.98; H, 3.93; N, 7.89%.

**General procedure for the preparation of ethyl 1-(3-chloro-4-flurophenyl)-1,2,3,4-tetrahydro-6-methyl-4-aryl-2-thioxopyrimidine-5-carboxylates (7a–j).** A mixture of ethyl acetoacetate **5** (1.30 g, 10 mmol), *N*-(3-chloro-4-fluoropheny) thiourea (**6**) (2.04 g, 10 mmol), different substituted aryl aldehydes **1a–j** (10 mmol), and iodine (5 mol%) in ethanol (15 mL) was stirred at room temperature till the reaction completed (4–6 h monitored by TLC). The reaction mixture was treated with 0.1 *N* $Na_2S_2O_3$ solution and extracted into ethyl acetate. The solvent was removed *in vacuo*; the resulting crude product was crystallized from ethanol to give the analytical pure compounds **7a–j**.

***Ethyl-1-(3-chloro-4-flurophenyl)-1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylate (7a).*** Yield 87%; mp 219–222°C; IR (KBr): 3384, 258, 3027, 2934, 1709, 1543, 1435, 748 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H, NH), 8.49–7.23 (m, 8H, Ar−H), 5.49 (s, 1H, CH), 4.68 (q, 2H, $CH_2$), 2.14 (s, 3H, $CH_3$), 1.04 (t, 3H, $CH_3$); MS: *m/z* = 405 [$M^+$]; Anal. Calcd. for $C_{20}H_{18}ClFN_2O_2S$: C, 59.33; H, 4.48; N, 6.92%. Found: C, 59.31; H, 4.47; N, 6.90%.

***Ethyl-1-(3-chloro-4-flurophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(2-nitrophenyl)-2-thioxopyrimidine-5-carboxylate (7b).*** Yield 81%; mp 211–213°C; IR (KBr): 3394, 3261, 3031, 2931, 1705, 1546, 1430, 750 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.04 (s, 1H, NH), 8.33–7.21 (m, 7H, Ar−H), 5.56 (s, 1H, CH), 4.76 (q, 2H, $CH_2$), 2.20 (s, 3H, $CH_3$), 1.22 (t, 3H, $CH_3$); MS: *m/z* = 450 [$M^+$]; Anal. Calcd. for $C_{20}H_{17}ClFN_3O_4S$: C, 53.39; H, 3.81; N, 9.34%. Found: C, 53.42; H, 3.86; N, 9.32%.

***Ethyl-1-(3-chloro-4-flurophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-thioxopyrimidine-5-carboxylate (7c).*** Yield 73%; mp 268–270°C; IR (KBr): 3378, 3265, 3033, 2927, 1711, 1540, 1460, 753 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H, NH), 8.56–8.47 (m, 7H, Ar−H), 5.53 (s, 1H, CH), 4.71 (q, 2H, $CH_2$), 2.23 (s, 3H, $CH_3$), 1.19 (t, 3H, $CH_3$); MS: *m/z* = 450 [$M^+$]; Anal. Calcd. for $C_{20}H_{17}ClFN_3O_4S$: C, 53.39; H, 3.81; N, 9.34%. Found: C, 53.41; H, 3.84; N, 9.33%.

***Ethyl-1-(3-chloro-4-flurophenyl)-1,2,3,4-tetrahydro-4-(3-methoxyphenyl)-6-methyl-2-thioxopyrimidine-5-carboxylate (7d).*** Yield 90%; mp 250–251°C; IR (KBr): 3397, 3269, 3026, 2939, 1714, 1547, 1450, 743 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H, NH), 8.27–7.19 (m, 7H, Ar−H), 5.51 (s, 1H, CH), 4.72 (q, 2H, $CH_2$), 3.91 (s, 3H, $OCH_3$), 2.17 (s, 3H, $CH_3$), 1.09 (t, 3H, $CH_3$); MS: *m/z* = 435 [$M^+$]; Anal. Calcd. for $C_{21}H_{20}ClFN_2O_3S$: C, 57.99; H, 4.64; N, 6.44%. Found: C, 57.94; H, 4.69; N, 6.47%.

***Ethyl-1-(3-chloro-4-flurophenyl)-1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-thioxopyrimidine-5-carboxylate (7e).*** Yield 77%; mp 286–288°C; IR (KBr): 3393, 3273, 3029, 2941, 1712, 1542, 1456, 739 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H, NH), 8.22–7.17 (m, 7H, Ar−H), 5.61 (s, 1H, CH), 4.78 (q, 2H, $CH_2$), 3.79 (s, 3H, $OCH_3$), 2.21 (s, 3H, $CH_3$), 1.13 (t, 3H, $CH_3$); MS: *m/z* = 435 [$M^+$]; Anal. Calcd. for $C_{21}H_{20}ClFN_2O_3S$: C, 57.99; H, 4.64; N, 6.44%. Found: C, 57.91; H, 4.67; N, 6.44%.

***Ethyl-1-(3-chloro-4-flurophenyl)-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate (7f).*** Yield 89%; mp 253–254°C; IR (KBr): 3407, 3168, 3081, 2975, 1742, 1537, 1428, 717 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H, NH), 8.23–7.13 (m, 7H, Ar−H), 5.57 (s, 1H, CH), 4.69 (q, 2H, $CH_2$), 2.11 (s, 3H, $CH_3$), 1.16 (t, 3H, $CH_3$); MS: *m/z* = 423 [$M^+$]; Anal. Calcd. for $C_{20}H_{17}ClF_2N_2O_2S$: C, 56.80; H, 4.05; N, 6.62%. Found: C, 56.77; H, 4.06; N, 6.61%.

***Ethyl-1-(3-chloro-4-flurophenyl)-4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate (7g).*** Yield 82%; mp 144–146°C; IR (KBr): 3403, 3111, 3076, 2926, 1704, 1568, 1440, 723 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H, NH), 8.46–7.25 (m, 7H, Ar−H), 5.47 (s, 1H, CH), 4.82 (q, 2H, $CH_2$), 2.15 (s, 3H, $CH_3$), 1.26 (t, 3H, $CH_3$); MS: *m/z* = 439 [$M^+$]; Anal. Calcd. for $C_{20}H_{17}Cl_2FN_2O_2S$: C, 54.68; H, 3.90; N, 6.38%. Found: C, 54.73; H, 3.87; N, 6.35%.

***Ethyl-1-(3-chloro-4-flurophenyl)-1,2,3,4-tetrahydro-4-(2-hydroxy-4-methoxyphenyl)-6-methyl-2-thioxopyrimidine-5-carboxylate (7h).*** Yield 85%; mp 246–248°C; IR (KBr): 3423, 3187, 3054, 2947, 1733, 1574, 1470, 741 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H, −NH), 8.17–7.09 (m, 7H, Ar−H), 5.37 (s, 1H, CH), 4.83 (s, 1H, OH), 4.53 (q, 2H, $CH_2$), 3.67 (s, 3H, $OCH_3$), 1.97 (s, 3H, $CH_3$), 1.24 (t, 3H, $CH_3$); MS: *m/z* = 451 [$M^+$]; Anal. Calcd. for $C_{21}H_{20}ClFN_2O_4S$: C, 55.94; H, 4.47; N, 6.21%. Found: C, 55.97; H, 4.53; N, 6.19%.

***Ethyl-1-(3-chloro-4-flurophenyl)-4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxylate (7i).*** Yield 76%; mp 264–266°C; IR (KBr): 3387, 3218, 3090, 2956, 1708, 1568, 1437, 739 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H, NH), 8.09–7.04 (m, 7H, Ar−H), 5.35 (s, 1H, CH), 4.61 (q, 2H, $CH_2$), 2.85 (s, 6H, $NCH_3$), 2.09 (s, 3H, $CH_3$), 1.29 (t, 3H, $CH_3$); MS: *m/z* = 448 [$M^+$]; Anal. Calcd. for $C_{22}H_{23}ClFN_3O_2S$: C, 58.99; H, 5.18; N, 9.38%. Found: C, 59.03; H, 5.22; N, 9.36%.

***Ethyl-1-(3-chloro-4-flurophenyl)-1,2,3,4-tetrahydro-6-methyl-4-(naphthalene-1-yl)-2-thioxopyrimidine-5-carboxylate (7j).*** Yield 78%; mp 257–259°C; IR (KBr): 3405, 3261, 3083, 2934, 1728, 1570, 1450, 736 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H, NH), 7.89–6.97 (m, 9H, Ar−H), 5.41 (s, 1H, CH), 4.58 (q, 2H, $CH_2$), 2.29 (s, 3H, $CH_3$), 1.32 (t, 3H, $CH_3$); MS: *m/z* = 455 [$M^+$]; Anal. Calcd. for $C_{24}H_{20}ClFN_2O_2S$: C, 63.36; H, 4.43; N, 6.16%. Found: C, 63.34; H, 4.41; N, 6.13%.

## CONCLUSIONS

In connection with our ongoing work on multicomponent domino synthesis and in view of our interest in the molecular iodine catalyzed reactions at ambient temperature, we now wish to report on a convenient and rapid one-pot three-component preparation of DHPMs derivatives with 5 mol % molecular iodine as a catalyst involving aromatic aldehydes **1a–j**, 1,3-diketone compound **3**, **5**, and thiourea **2**, **6**. Iodine may play a crucial role in accelerating the dehydrative steps and enolization of 1,3-diketone compounds, in which the 4- and 5-positions of the DHPMs **4a–j** and **7a–j** have been substituted with a variety of groups. We have demonstrated a simple route for the synthesis of 1-substituted DHPMs. This methodology offers very attractive features such as short reaction time, mild reaction condition, good to excellent product yields, minimum environmental effects, and commercially available iodine as a powerful catalyst; the use of iodine was well tolerated with a range of aldehydes. This protocol is general and provides DHPMs in good to excellent yields depending on the reactivity of arylaldehydes.

Some of the newly synthesized compounds **4d** (**3-$OCH_3$**), **4f** (**4-F**), and **7e** (**4-$OCH_3$**) exhibited good antimycobacterial and antibacterial activities against *E. coli*, *S. aureus*, and *P. aeruginosa* as well as antifungal activity against *C. albicans*.

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