chemistry proceedings

Proceedings Paper

# An Efficient Synthesis and Antibacterial Activity of Some Novel 3,4–Dihydropyrimidin-2-(*1H*)-Ones †

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† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

**Abstract:** We have efficiently synthesized mono as well as bis and also spiro cyclic products of 3,4-dihydropyrimidin-2(*1H*)-ones (DHPMs) by refluxing a reaction mixture of the three components in Deep Eutectic Solvent (*DES*) to generating "libraries from libraries". Synthesized Spiro fused heterotricyclic compounds containing urea moiety is potent against bacteria. Overall antibacterial study, from the synthesized compounds. Some of 3,4–dihydropyrimidin-2-(*1H*)-ones compounds were found to possess anti-bacterial efficacy.

**Keywords:** 3,4-dihydropyrimidin-2(*1H*)-ones; bis-dihydropyrimidinones; spirofused heterotricyclic; Deep Eutectic Solvent and Antibacterial activity

**Citation:** Pawar, N.S.; Patil, P.N.; Pachpande, R.N. An Efficient Synthesis and Antibacterial Activity of Some Novel 3,4–Dihydropyrimidin-2-(*1H*)-Ones. *Chem. Proc.* **2021**, *3*, x. https://doi.org/10.3390/xxxxx

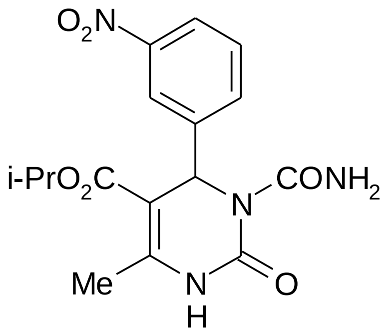
Academic Editor: Julio A. Seijas

Published: 15 November 2021

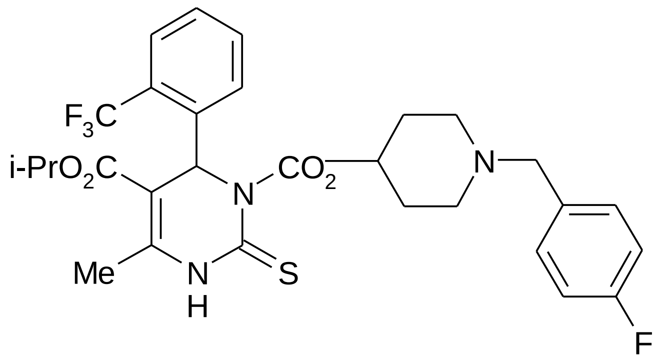


## 1. Introduction

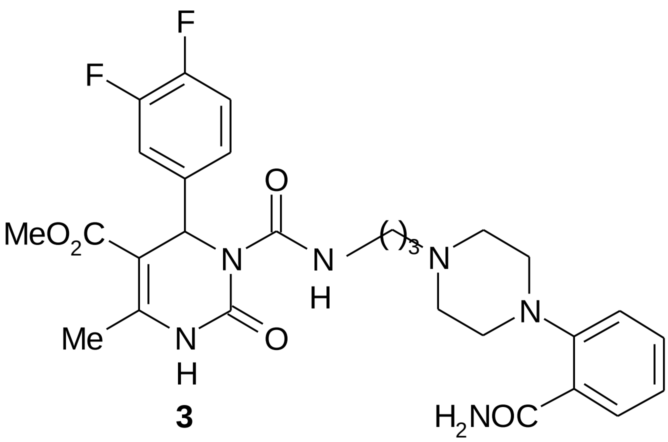
A tremendous increase in activity has occurred, as evidenced by the growing number of publications and patents on the subject of Biginelli reaction i.e., 3,4-dihydropyrimidin-2-(*1H*)-one. This is mainly due to the fact that the multi functionalized dihydropyrimidine scaffold (DHPMs, "Biginelli compounds") represents a heterocyclic system of remarkable pharmacological efficiency. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities, has been ascribed to these partly reduced pyrimidinederivatives [1]. More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents (**5**,**6**) [2–4] or $\alpha_{1a}$ adrenoceptor-selective antagonists (**3**) [5]. A very recent highlight in this context has been the identification of the structurally rather simple DHPM monastrol (**4**) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest [6]. Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs [6]. Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated [7]. Most notable among these are the batzelladine alkaloids A and B (e.g., **5**), which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy [8].

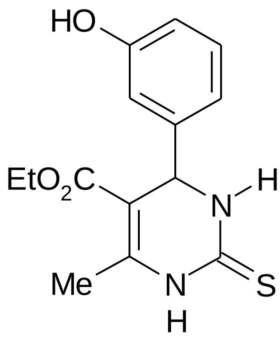


**1**, SQ 32926

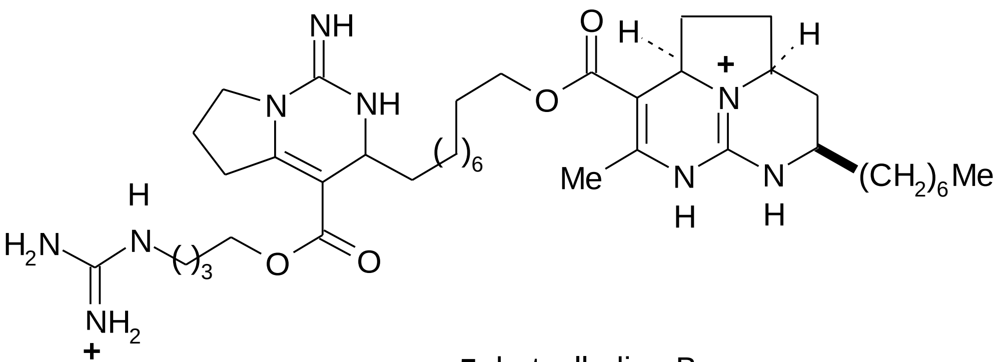


**2**, SQ 32547





**4,** monastrol



**5**, batzelladine B

Now a day there is a great variety of suitable reaction conditions for Biginelli condensations have been reported including classical conditions with microwave irradiation and by using Lewis acids, as well as protic acids, as promoters. Such promoters as conc. HCl [9], $BF_3$•$OEt_2$ [10], PPE [9], KSF clay [11], $InCl_3$ [12], $LaCl_3$ [13], lanthanide triflate [14], $H_2SO_4$ [13], ceric ammonium nitrate (CAN) [15], $Mn(OAc)_3$ [16] ion-exchange resin [17], 1-n-butyl-3-methyl imidazolium tetrafluoroborate ($BMImBF_4$) [18], $BiCl_3$ [19], $LiClO_4$ [20], $InBr_3$ [21], $FeCl_3$ [22], $ZrCl_4$ [23], $Cu(OTf)_2$ [24], $Bi(OTf)_3$ [25], LiBr [26], ytterbium triflates [27], $NH_4Cl$ [28,29], $CdC1_2$ [30], TMSCl [31], $RuCl_3$ [32], NBS [33], etc. have been found to be effective and these methods tack the simplicity of the original one-pot Biginelli protocol.

However, some of these methods require the use of toxic reagents in combination with Bronsted acids, such as hydrochloric acid and acetic acid, as additives. Many of these methods involve expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields and incompatibility with other functional group.

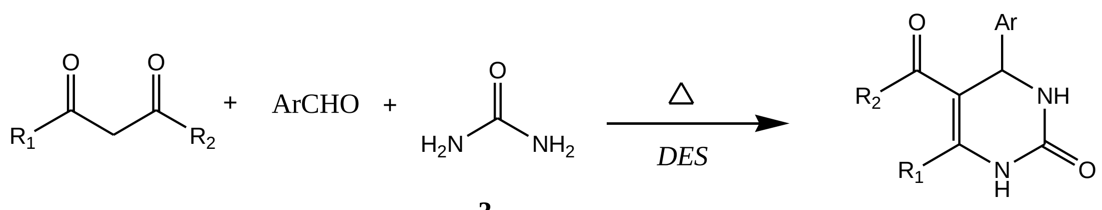
The synthesis of DHPMs is thus of significant importance in organic synthesis due to their wide range of biological activities. In view of our interest to develop greener protocols for organic transformations, we herein report the application of *DES* ($K_2CO_3$ + Glycerol, 1:5) as catalysts as solvent for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using a multicomponent condensation approach. Also a large and exciting extension of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) to new reaction utilizing parallel organic synthesis arrays, as demonstrated by the use of easily and cheaply available *DES* ($K_2CO_3$ + Glycerol, 1:5), the potential of the spirocyclic products for generating "libraries from libraries".

## 2. Results and Discussion

*DES* ($K_2CO_3$+Glycerol), ethyl acetoacetate, acetyl acetone, cyclohexanone, urea, thiourea and aromatic aldehydes [Benzaldehyde, Vanillin, Cinnamaldehyde and Terphthaldehyde] obtain from s.d. Fine Chemical Ltd. India. Melting points were determined using open capillary method in the paraffin liquid and are uncorrected. IR spectra were recorded on a Perkin Elmer FTIR spectrophotometer. $^1$H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. The FAB mass spectra were recorded on a Jeol SX 102/Da-600 mass spectrometer. Reactions were monitored by TLC using $CHCl_3$:EtOH, [9:1] solvent system. All the products were characterized by comparing their IR, $^1$H NMR, MS and melting points with those reported in literature.

### 2.1. General Procedure for Synthesis of Dihydropyrimidinones

A solution of an appropriate ethyl acetoacetate/acetyl acetone (1.2 mmol), corresponding aldehyde (1.0 mmol), urea (1.2 mmol), and *DES* ($K_2CO_3$+Glycerol) (20 mL) was heated under reflux for several hours (completion of reaction was monitored by TLC). The reaction mixture was washed thoroughly with water, filtered and recrystallized from methanol to afford pure product. [Scheme 1 and Table 1].




**Scheme 1.** Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.

**Table 1.** Synthesis of 3, 4-dihydropyrimidin-2(1*H*)-ones.

| Entry * | R1 | R2 | Ar | Products | Reaction Time (h) | Yield # (%) | m.p. (°C) |
|---|---|---|---|---|---|---|---|
| 1 | $CH_3$ | $OC_2H_5$ | $C_6H_5$- | 4a | 2 | 81 | 204-205 |
| 2 | $CH_3$ | $CH_3$ | $C_6H_5$-CH=CH- | 4b | 1.5 | 80 | 171-173 |
| 3 | $CH_3$ | $OC_2H_5$ | $C_6H_5$-CH=CH- | 4c | 1.5 | 76 | 231-232 |
| 4 | $CH_3$ | $CH_3$ | *p*-OH,*m*-$OCH_3$ $C_6H_5$- | 4d | 3 | 75 | 210-213 |
| 5 | $CH_3$ | $OC_2H_5$ | *p*-OH,*m*-$OCH_3$ $C_6H_5$- | 4e | 3 | 81 | 233-235 |
| 6 | $CH_3$ | $OC_2H_5$ | -$C_6H_5$CHO | 4f | 5 | 70 | >300 |

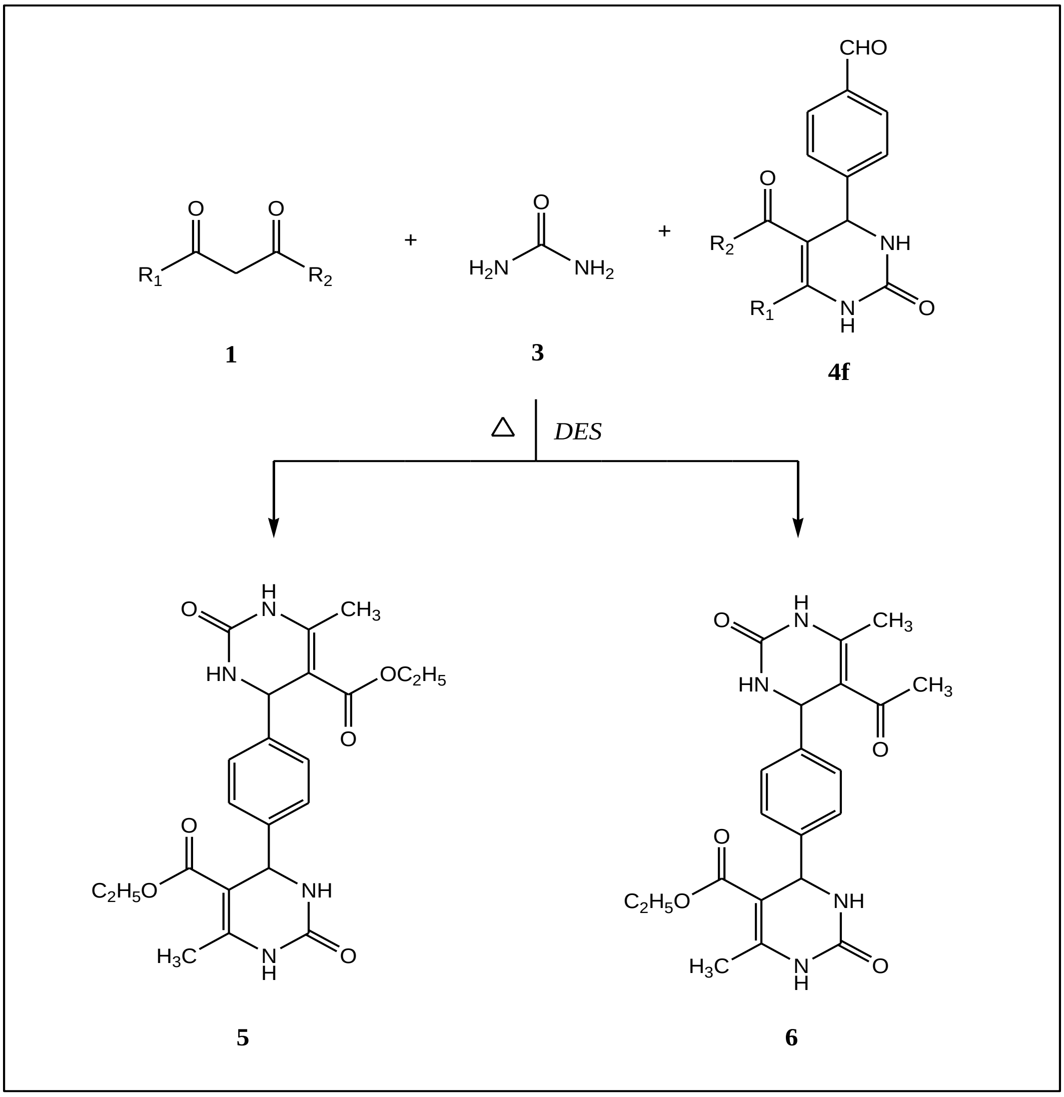
* All product were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature [1,2,5,34–36] # Isolated yields. The spectral data of the some of the compounds are given below: Entries 2 and 4 (4b and 4d), the spectroscopic data is full agreement with the literature data. **IR data: Frequency ($cm^{-1}$): Entry 1: (4a)** 3238, 3117, 2980, 1722, 1697, 1644, 1462, 1419, 1383, 1367, 1340, 1313, 1289, 1272, 1217, 1180, 1087, 1027, 956, 879, 824, 756, 697, 661. **Entry 3: (4e)** 3335, 3342, 3098, 2978, 1689, 1642, 1492, 1373, 1121, 785. **Entry 6: (4f)** 2924, 2854, 1699, 1646, 1446, 1405, 1377, 1331, 1232, 722. **$^1$H NMR data (DMSO-$d_6$): Entry 1: (4a)** δ = 9.18 (s, 1H, NH), 7.74 (s, 1H, NH), 7.22 (m, 5Harom), 5.14 (d, 1H, J = 3.6 $H_2$, H-4), 3.40 (q, 2H, J = 6.9 $H_2$, $OCH_2$), 2.24 (s, 3H, $CH_3$), 1.09 (t, 3H, J = 6.9 $H_2$, $CH_3$). **Entry 3: (4c)** δ = 1.06 (t, 3H, J = 7.0 Hz), 2.50 (s, 3H), 3.95 (q,2H, J = 7.0 $H_2$), 4.24 (d, 1H, J = 6.0 $H_2$), 6.05 (dd, 1H, J = 16.4 Hz), 6.2 (d, 1H, J = 16.4 Hz), 7.25 (m, 5H) 7.45 (d, NH, J = 1.7 HZ), 8.95 (br, S, NH), **Entry 5: (4e)** δ = 1.093 (t, 3H, $CH_3$-$CH_2$), 2.245 (S, 3H, $CH_3$-C) 3.272 (s, 3H, $CH_3$-O), 3.989 (q, 2H, -$CH_2$), 5.073 (S, 1H, -OH), 6.722 (m, 3H, Ar-H), 7.623 (S, NH), 8.891 (S, NH). **Entry 6: (4f)** δ = 1.058 (t, 3H, $CH_3$-$CH_2$O), 1.199 (S, 3H, $CH_3$-C), 3.943 (q, 2H, -$CH_2$-O), 5.111 (S, 1H, OH), 7.160-7.869 (m, 4H, Ar-H), 9.076 (S, NH), 9.933 (S, 1H, CHO-). **MS data: Entry 1 (4a):** (ES/MS): m/z 259 (M-H), **Entry 3 (4c):** (EIMS): m/z 286 ($M^+$) 252, 224, 196, 149, 84.

### *2.2. Synthesis of Bis-Dihydropyrimidinones*

The terphthaldehyde is a interesting class of bis aldehyde compounds which have two active site at which reaction is take place i.e., two-CHO groups. The literature survey indicates that, no lot of work has been done on terphthaldehyde so that we have been done work on both active site of terphthaldehyde.

### *2.3. General Procedure for Synthesis of Bis-Dihydropyrimidiones*

The mixture of an aldehyde (1.0 mmol) urea (1.2 mmol), ethyl acetoacetate/acetyl-acetone (1.2 mmol) and and *DES* ($K_2CO_3$+Glycerol) (25 mL) was heated under reflux on water bath for 4~5 h. The completion of reaction was monitored by TLC further the reaction mixture was cooled and poured on crushed ice. The solid was separated out and then filtered, washed with pet. ether, dried and recrystallized using ethanol [Scheme 2 and Table 2].




**Scheme 2**. Synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-ones.

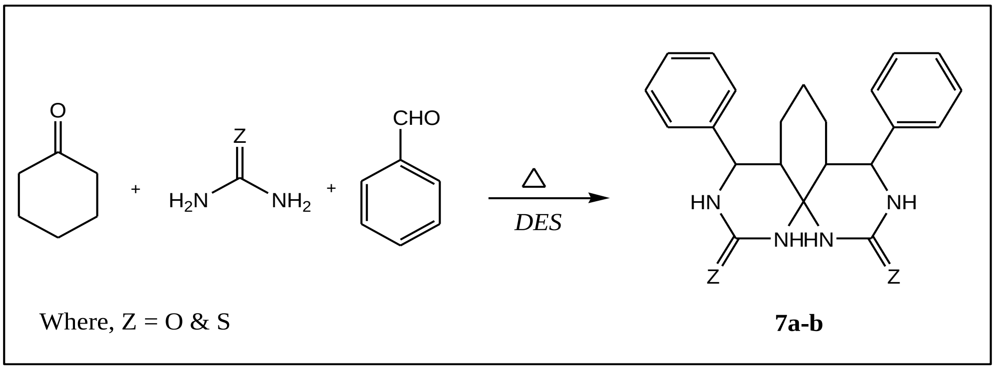
**Table 2.** Synthesis of bis-3,4-dihydropyrimidin-2(1*H*)-ones.

| **Entry*** | **R₁** | **R₂** | **Products** | **Reaction Time (hrs)** | **Yield# (%)** | **m.p. (ºC)** |
|---|---|---|---|---|---|---|
| 7 | $CH_3$ | $OC_2H_5$ | 5 | 5 | 75 | >300 |
| 8 | $CH_3$ | $CH_3$ | 6 | 4 | 65 | >300 |

* All product were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature; # Isolated yields. The spectral data are given below: **IR data: Frequency (cm$^{-1}$): Entry 8 (6):** 2924, 2854, 1699, 1655, 1459, 1406, 1377, 1331, 1230, 1087, 801. **$^1$H NMR data (DMSO-d$_6$): Entry 7 (5):** 1.075 (t, 3H, $CH_3$-$CH_2O$), 2.213 (s, 3H, $CH_3$-C), 3.945-3.961 (q, 2H, -$CH_2$-O), 5.114 (s,. 1H, -CH), 7.161-7.869 (m, 4H, Ar-H), 9.075 (s, NH), **Entry 8 (6):** 1.058 (t, 3H, $CH_3$-$CH_2O$), 1.139 (s, 3H, $CH_3$-C), 2.214 (s, 3H, $CH_3$-CO-), 3.945-3.962 (q, 2H, -$CH_2$-O-), 5.114 (s, 1H, -CH), 7.160-7.870 (m, 4H, Ar-H), 9.074 (s, NH) **MS data: Entry 7 (5)**: (ES/MS): m/z 441 (M-H), 441, 397, 259, 183, 89.

### *2.4. Synthesis of Spirofused Heterotricyclic Compounds*

To a mixture of cyclohexanone (2.1 mL, 5.0 mmol), benzaldehyde (4.6 mL, 10.0 mmol), urea (4.1 gm, 15.0 mmol) or thiourea (4.6 gm, 15.0 mmol) and *DES* ($K_2CO_3$+Glycerol) (25 mL) with stirring. The resulting mixture was refluxed for 6 h. After completion of reaction as monitored by TLC using $CHCl_3$:EtOH, (8:2) solvent system, then reaction mixtures was cooled and pour into crushed ice and filtered. The crude residue was washed with pet. ether and then recrystallized with alcohol to afford the desired spiro fused heterotricyclic compound. [Scheme 3 and Table 3].




**Scheme 3.** Spirofused heterotricyclic compounds.

**Table 3.** Synthesis of Spiro fused heterotricyclic compounds.

| Entry* | Z | Products | Reaction Time (hrs) | Yield# (%) | m.p. (ºC) |
|---|---|---|---|---|---|
| 9 | O | 7a | 6 | 75 | 328 |
| 10 | S | 7b | 6 | 78 | >360 |

*All products were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature. # Isolated yields. The spectral data given below: **MS data**: **Entry 10 (7b):** (EIMS): m/z 409 ($M^+$) 409, 333, 245, 154, 91.

Antibacterial Activity

Bioassay is important and crucial method in evaluation of bio-activity of the compounds and helpful to establish structure-activity relationship (SAR). In present work, all the synthesized compounds have been tested for their anti-bacterial potency against different bacterial species.

The bacterial potency is proportional to the diameter (in mm) of the zone of inhibition. The experiments were performed in duplicate and the average of the measured zones of inhibitions was considered and the results were summarized in Tables 4 and 5.

**Table 4.** Antibacterial activity data of 3,4-dihydropyrimidin-2-(*1H*)–ones.

| Entry | Compounds | Zones of Inhibition in mm at Concentration of 20 µg/mL | | | |
|---|---|---|---|---|---|
| | | *E. coli* | *P. vulgaris* | *S. aureus* | *B. subtilis* |
| 1 | 4a | — | — | — | — |
| 2 | 4b | — | — | — | — |
| 3 | 4c | — | — | — | — |
| 4 | 4d | — | — | — | — |
| 5 | 4e | — | 03 | — | 03 |
| 6 | 4f | — | — | 01 | — |
| 7 | 5 | — | — | 04 | — |
| 8 | 6 | — | — | — | — |

**Table 5.** Antibacterial activity data of spiro fused heterotricyclic compounds.

| Entry | Compounds | Zones of Inhibition in mm at Concentration of 20 μg/mL | | | |
|---|---|---|---|---|---|
| | | ***B. subtilis*** | ***S. aureus*** | ***P. vulgaris*** | ***P. acurginosa*** |
| 9 | 7a | 07 | 9 | 15 | 06 |
| 10 | 7b | 17 | 15 | 19 | 09 |

In overall antibacterial study, from the synthesized compounds **4a-f, 5** and **6,** some of 3,4–dihydropyrimidin-2-(*1H*)-ones compounds were found to possess anti bacterial efficacy. No any trend was observed between structural modification and antibacterial action to postulate any hypothesis. Among all synthesized compounds, **4e** may be due to *p*-OH and *m*-$OCH_3$ containing groups of benzene ring and **4f** and **5** these may be due to—CHO group possesses in benzene ring, exhibited remarkable antibacterial efficacy.

While in case of synthesized spirofused heterotricyclic compounds (**7a,b**), compound **7a** containing urea moiety is potent against bacteria but compound **7b** containing thiourea moiety is more potent against tested all four bacterial species as compare to compound **7a**.

## 3. Conclusions

In the present investigation, a reaction mixture consisting of aryl or aliphatic aldehydes, urea and ethyl acetoacetate or acetyl acetone in presence of *DES* at heating condition only (Tables 1 and 2), because, first of all we observe these reactions at room temperature but it doesn't get target products. After completion of reaction, the homogeneous mixture pour in cold water and tend to the isolation of pure mono as well as bis 3,4-dihydropyrimidin-2(1*H*)-one in good yield. The amount of *DES* ($K_2CO_3$+Glycerol) molar ratio 1:5, we have been fixed on the basis of up to the obtained well homogeneity of all the three-components.

The classical Biginelli reaction is considerably extended use of cycloalkanones instead of 1,3-dicarbonyl compounds. The versatility of the method was then checked by using thiourea and urea to prepare spiro fused heterotricyclic compound (Table 3). Both these variation did not affect appreciably as the yield as well as ease of work up procedure, only it needs purification more only.

In presence of *DES* ($K_2CO_3$+Glycerol), the Biginelli reaction satisfactory fulfills the entire above requirement. *DES* here we use that one also cheaply and shelf availability reagent. *DES* are soluble in water and easily removed by simple workup procedure and it can be reuse up to three to four times well.

**Institutional Review Board Statement:**

**Informed Consent Statement:**

**Data Availability Statement:**

**Acknowledgments:** Authors are very thankful to Principal J. S. Rane, Pratap College, Amalner for providing necessary laboratory facilities and also to SAIF, CDRI, Lucknow, INDIA, for providing a necessary valuable data of all the synthesized compounds.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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