al Kimiya: Jurnal Ilmu Kimia dan Terapan
p-ISSN: 2407-1897, e-ISSN: 2407-1927
Vol. 12, No. 1 (35-40), June 2025/Muharram 1447

SOLVENT-FREE SYNTHESIS OF DIHYDROPYRIMIDINONE BY USING MOLECULAR IODINE AS CATALYST

ARIF FADLAN[1*], LANDAETA YOLGA PRATAMA[1], AND YAN ALAMANDA ILFAHMI[1]

[1]Department of Chemistry, Faculty of Science and Data Analytics, Institut Teknologi Sepuluh Nopember, Teknik Kimia Street, Keputih, Sukolilo, Surabaya, Jawa Timur 60111, Indonesia

*Corresponding Author email: afadlan@its.ac.id

Article Information

Received: Dec 18, 2024
Revised: Apr 28, 2025
Accepted: Jun 12, 2025
Published: Jun 30, 2025

DOI: 10.15575/ak.v12i1.42254

Keywords:
Dihydropyrimidinone; Iodine; Solvent-free.

Abstract

Dihydropyrimidinone with diverse pharmacological activities can be obtained through the multicomponent of Biginelli reactions by heating aldehyde, ethyl acetoacetate and urea/thiourea in ethanol with the addition of hydrochloric acid. However, this reaction is toxic and shows several drawbacks. Further development for Biginelli reaction was conducted by using heterogeneous catalyst, green solvents, and sustainable heating such as microwave or ultrasound. But various obstacles are also found from these strategies. There are still chances to study the Biginelli reaction by using relatively simpler methods and the readily available and environmentally friendly chemicals. Iodine is a mild Lewis acid, easily available at an affordable price, non-toxic, and environmentally friendly. Iodine has been used in various reactions and organic transformations with high efficiency and selectivity. This report aims to study the solventless synthesis of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **4** by using molecular iodine. The reaction was studied by mixing benzaldehyde **1** as aromatic aldehyde, urea **2**, and β-keto ester in the form of ethyl acetoacetate **3** with and without the addition of ethanol as solvent. The compound **4** (45% yield) was yielded from a solvent-free reaction whereas the use of ethanol gave the product **4** in 50%yield. The IR, NMR spectra, and HRMS analysis were used for the establishment of the structure of product **4**. These finding give new perspective in the preparation of dihydropyrimidinone(s).

INTRODUCTION

Dihydropyrimidinone containing one carbonyl group and two nitrogen atoms in a six-membered ring is an important heterocyclic compound with diverse pharmacological activities [1-3]. Methylthiouracil, idoxuridine, 5-fluorouracil, emivirine, and riboflavin are drugs with dihydropyrimidinone framework that are found commercially in the market. Monastrol, one of the anticancer drugs, contains a dihydropyrimidinone structure which is still being developed [3].

Generally, dihydropyrimidinone can be obtained via the multicomponent of Biginelli and Hantzsch reactions [4]. The Hantzsch reaction involving benzaldehyde, β-ketoester ethyl acetoacetate and ammonia produces 1,4-dihydropyrimidine [5], while Biginelli reaction is generally carried out by heating the aldehyde, ethyl acetoacetate and urea/thiourea in ethanol with the addition of hydrochloric acid as a catalyst to produce 3,4-dihydropyrimidinone [6-7]. However, the Biginelli reaction shows shortcomings, such as the reaction takes a relatively long time under heating, the reaction temperature being relatively high, the use of environmentally unfriendly strong acid catalysts, and the relatively low yield of products [8-9]. Thus, the chance of the development of Biginelli reaction is still open to overcoming these problems.

Various strategies have been conducted for the development of Biginelli reaction. This reaction was successfully carried out by using heterogeneous catalysts to replace the homogeneous and toxic Bronsted and Lewis acid catalysts [10]. The heterogeneous catalysts used include magnesium (II) chloride [11], tin (II) chloride [12], hafnium (IV) triflatic acid [13], $H_5PV_2W_{10}O_{40}$ [14], cerium trifluoromethanesulfonate [15], iodine [16], and $ZnCr_2O_4$ [17]. Other studies revealed the use of green solvents for the synthesis of dihydropyrimidinones via Biginelli reaction [18]. A study on Biginelli reaction under sustainable heating (microwave or ultrasound) was also conducted [19]. The development of Biginelli reaction generates dihydropyrimidinones with different yields with their advantages. However, these works also show some shortcomings, such as the use of toxic heterogeneous catalysts, relatively high reaction temperatures and relatively low

yields for some products [20]. As a result, there are still voids to study the Biginelli reaction by using relatively simpler methods and the readily available and environmentally friendly chemicals.

Iodine is a halogen element with similar reactivity as transition metal derivatives, but iodine is cheaper and more environmentally friendly [21]. Iodine as a soft Lewis acid catalyst has been used in various reactions and organic transformations with high efficiency and selectivity. It works in dilute solutions and reactions with high concentrations to solvent-free conditions compared to other Lewis acid catalysts, especially metal catalysts [22]. Moreover, iodine is easily available at an affordable price and is non-toxic. Iodine has been used in the synthesis of alkenes by dehydration of tertiary alcohols, the formation of β-keto-enol ether, esterification reactions, trans-esterification, acetylation and the formation of benzothiophenone. Literature study indicates the information on the solvent-free synthesis of dihydropyrimidinone by using molecular iodine as catalyst is still very limited or has never been reported. Therefore, this study aims to study the solventless synthesis of dihydropyrimidinones by using molecular iodine. In this study, ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **4** was obtained from a reaction of benzaldehyde **1**, urea **2** and ethyl acetoacetate **3**. The reaction was studied with and without solvents.

EXPERIMENT

Material

Benzaldehyde **1**, urea **2**, and ethyl acetoacetate **3** were obtained from a commercial supplier for synthesis grade (SigmaAldrich, USA). Sodium thiosulfate and solvents (ethanol, ethyl acetate, *n*-hexane) were purchased as pro analysis grade (Merck, Germany; Fulltime, USA; Tedia, USA). Thin layer chromatography (TLC) was performed on silica gel 60 F254 (Merck, Germany) with UV lamps (Desaga, Germany) visualization.

Instrumentation

Fisher John *melting point apparatus* (Fisher Scientific, USA) was used for melting point measurement and uncorrected. ^{1}H NMR were recorded on Agilent 500 MHz spectrometer (Bruker, Switzerland). Infrared spectra were obtained from the FTIR Shimadzu-8400S spectrometer (Shimadzu, Japan). Mass spectra were collected in Thermo Scientific TSQ Vintage Triple State Quadrupole MS (Shimadzu, Japan).

Procedure

*Synthesis of Dihydropyrymidinone (ethyl 4-phenyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate **4**)*

With solvent

Iodine (5mol%) was added to the solution of benzaldehyde **1** (9.4 mmol), urea **2** (9.4 mmol), and ethyl acetoacetate **3** (10 mmol) in ethanol (10 mL). The reaction was performed at reflux and stopped as indicated by TLC monitor. The mixture was cooled and mixed with 5% $Na_2S_2O_3$. The formed solid was filtered, washed (cold water), and dried. The solid was recrystallized from ethanol to give the product **4** as a white solid (1.23 g, 50% yield); mp 239–240°C; IR (KBr): *v* 3244, 3177, 1703, 1724, 1645, 1290, 1092 cm^{-1}; ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 500 MHz): δ 9.23 (s, 1H, NH), 7.77 (s, 1H, NH), 7.23-7.34 (m, 5H, ArH), 5.14 (s, 1H, CH), 4.00 (q, J = 7; 7.5 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.10 (t, J = 7 Hz, 3H, CH_3), HRESIMS [Found: *m*/*z* 261.1223 $(M+H)^+$, calcd. for $C_{14}H_{17}N_2O_3$: $(M+H)^+$, 261.1239].

Without solvent

A 5 mol% of iodine crystal was added to a round bottom flask containing benzaldehyde **1** (9,4 mmol), urea **2** (9,4 mmol), dan ethyl acetoacetate **3** (10 mmol). The reaction mixture was stirred at 133°C for 5 hours (TLC monitor). The cooled mixture was then treated with saturated aqueous $Na_2S_2O_3$ (20 mL) and left overnight. The mixture was separated by filtration and the obtained solid was purified by recrystallization from ethanol to give the product **4** as a white solid (1.16 g, 47% yield); mp 238–239°C; IR (KBr): *v* 3244, 3177, 1724, 1703, 1645, 1290, 1092 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.17 (s, 1H, NH), 7.72 (s, 1H, NH), 7.23-7.33 (m, 5H, ArH), 5.14 (d, J = 3 Hz, 1H, CH), 3.98 (q, J = 7; 7.5 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.09 (t, J = 7 Hz, 3H, CH_3), HRESIMS [Found: *m*/*z* 261.1223 $(M+H)^+$, calcd. for $C_{14}H_{17}N_2O_3$: $(M+H)^+$, 261.1239].

RESULT AND DISCUSSION

Synthesis of Ethyl 4-Phenyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate 4

In this study, the straightforward reaction that takes place when aromatic aldehyde **1**, urea **2**, and β-keto ester **3** were combined to produce

dihydropyrimidinone **4** is possible to be explained by assuming the sequence shown in **Figure 1**. The reaction was performed with and without solvent with the addition of molecular iodine. Surprisingly, the product dihydropyrimidinone **4** was generated from the reaction with the absence of solvent.

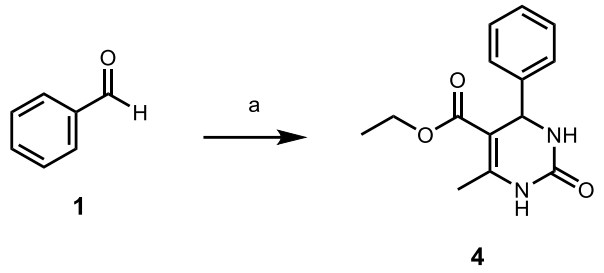
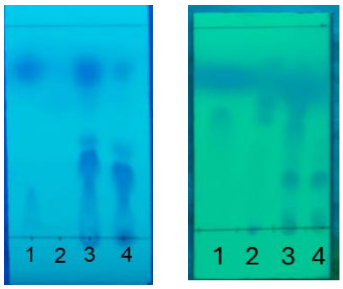


Figure 1. Synthesis of dihydropyrimidinone **4**. Reagents/conditions: urea **2**, ethyl acetoacetate **3**, molecular iodine, reflux or 133°C, 50% (with solvent), 45% (without solvent).

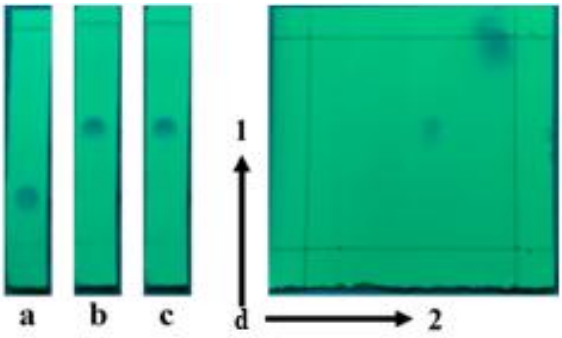
The synthesis of dihydropyrimidinone **4** with solvent was carried out by reacting compound **1**, **2**, and **3** in ethanol. The molecular iodine as catalyst was then added and the reaction mixture was refluxed. A similar reaction without solvent was performed with the same reagents in a round bottom flask with the addition of iodine crystals. The reaction mixture was stirred at 133°C. The TLC monitor (*n*-hexane:ethyl acetate 1:1) as shown in **Figure 2** indicated the formation of a new spot with a different retardation factor from that of starting materials. The reaction was then stopped, and the reaction mixture was further treated with $Na_2S_2O_3$ solution. The obtained solid was separated by filtration and purified by recrystallization to produce the dihydropyrimidinone **4** in 50% and 45 % yields for reactions with and without solvent, respectively.



1. benzaldehyde **1**
2. ethyl acetoacetate **2**
3. mix of **1** + **2** + reaction mixture
4. reaction mixture

Figure 2. TLC monitor profile of synthesis dihydropyrimidinone **4** under UV 254 nm. A = with solvent, B = without solvent.

The purity of the resulting solids was then tested by using TLC and a melting point test. **Figure 3** shows that it resulted in a single spot indicating that the solids are pure. The melting point test which produces a narrow difference (1–2ºC) supports the purity check by TLC [23].



a. *n*-hexane:ethyl acetate 1:1
b. *n*-hexane:ethyl acetate 1:7
c. ethyl acetate
d. (1) *n*-hexane:ethyl acetate 1:4
(2) *n*-hexane:ethyl acetate 1:5

Figure 3. TLC profile of dihydropyrimidinone **4.**

Characterization of Ethyl 4-Phenyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate 4

Reaction of benzaldehyde **1**, urea **2**, and ethyl acetoacetate **3** produced dihydropyrimidinone **4** as white solids. The ^{1}H NMR spectrum in DMSO-d_6 (500 MHz) indicated the presence of NH protons as two singlets at δ 9.17 ppm and δ 7.72 ppm. The methyl protons appeared as triplet and singlet signals at δ 1.09 ppm and δ 2.25 ppm, respectively. A quartet signal at δ 3.98 ppm (J = 7;7.5 Hz) and a doublet signal at δ 5.14 ppm (J = 3 Hz) attributed to CH_2 and CH protons. The aromatic protons presented as multiplet signals at δ 7.33-7.23 ppm (**Figure 4**). **Table 1** displays the ^{1}H NMR data of **4**.

The formation of dihydropyrimidinone **4** deduced from ^{1}H NMR data was supported by infrared analysis. The IR spectrum displayed the NH group as absorptions at v 3244 cm^{-1} and 3177 cm^{-1}, respectively. The carbonyl group appeared as peaks at v 1724 cm^{-1} and 1703 cm^{-1}. The bands at v 1645, 1290, and 1092 cm^{-1} corresponded to C=C and C-O bonds. The HRESIMS analysis revealed the molecular mass of dihydropyrimidinone **4** as molecular ion (m/z) $[M+H]^+$ peak at m/z 261.1223 for $C_{14}H_{17}N_2O_3$ associates to the theoretical m/z $[M+H]^+$ 261.1239.

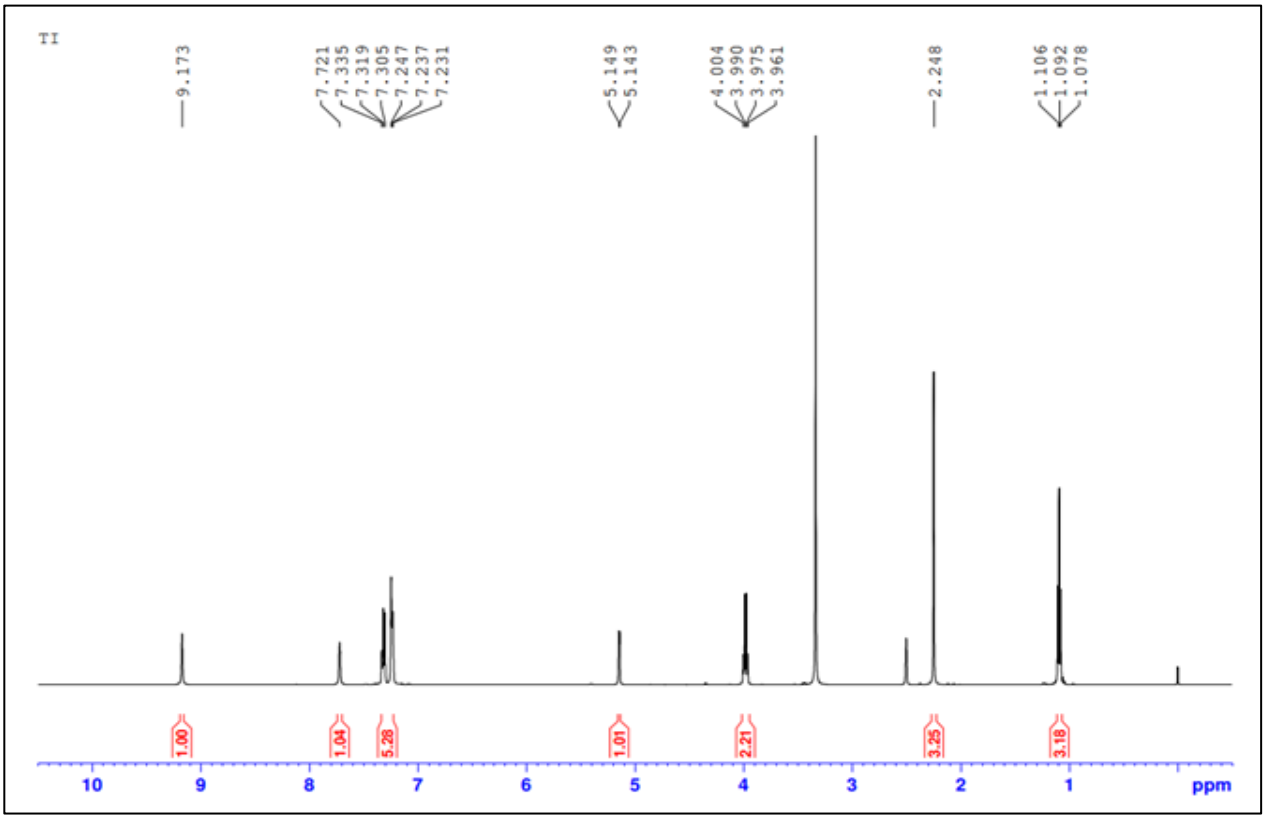


Figure 4. [1]H NMR spectrum of dihydropyrimidinone **4.**

Table 1. [1]H NMR data of dihydropyrimidinone **4.**

Protons	Chemical Shifts (δ) (ppm)	
	This work	[24]
NH	9.17 (s, 1H)	9.20 (s, 1H)
NH	7.72 (s, 1H)	7.75 (s, 1H)
Ar H	7.23-7.33 (m, 5H)	7.28 (m, 5H)
CH	5.14 (d, J = 3 Hz, 1H)	5.14 (s, 1H)
OCH_2	3.98 (q, J = 7; 7.5 Hz, 2H)	3.97 (q, J = 7.1 Hz, 2H)
CH_3	2.25 (s, 3H)	2.25 (s, 3H)
CH_3	1.09 (t, J = 7 Hz, 3H)	1.09 (t, J = 7.1 Hz, 3H)

Proposed Reaction Mechanism for The Formation of Ethyl 4-Phenyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate 4

Figure 5 envisaged the presumable mechanism for the establishment of dihydropyrimidinone **4**. At the first step of reaction, it is predicted that molecular iodine activated benzaldehyde. Subsequently, the condensation of the activated benzaldehyde with keto-imine urea tautomer occurs to give **I**, followed by removal of a water molecule to give the iminium intermediate **II**. This intermediate may further react with ethyl acetoacetate molecule in the next step and by the similar pathway giving product **4**.

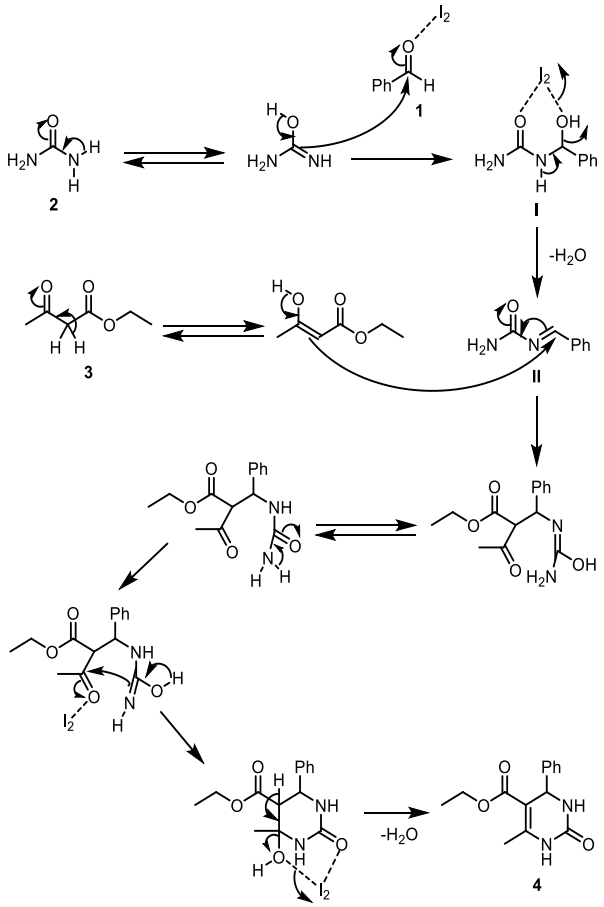


Figure 5. Proposed mechanism for the synthesis of dihydropyrimidinone **4.**

CONCLUSION

In conclusion, dihydropyrimidinone **4** was produced in 45% yield from a reaction without a solvent. The structure of the product was established by IR, NMR spectra, and HRMS analysis. A plausible mechanism was also proposed.

ACKNOWLEDGEMENT

The authors wish to thank The Ministry of Education, Culture, Research, and Technology Indonesia for providing financial support in the form of Penelitian Tesis Magister (1823/PKS/ITS/2024).

REFERENCES

[1] L.H.S. Matos, F.T. Masson, L.A. Simeoni, and M. Homem-de-Mello, "Biological activity of dihydropyrimidinone (DHPM) derivatives: A systematic review", *European Journal of Medicinal Chemistry*, **143**, 1779–1789, 2018, https://doi.org/10.1016/j.ejmech.2017.10.073

[2] L. Benazir Ali, A. Subramani, V.S. Jamal Ahamed, Priya V. Patel, T.K. Shabeer, P. Tamizhdurai, Asad Syed, Hind Al-Shwaiman, and P. Sasikumar, "*In silico* investigation and biological evaluation *viz* antimicrobial, genotoxic, and anticancer potentials of new dihydropyrimidinones (DHPMs) synthesized by Biginelli reaction", *Journal of Molecular Structure*, **1316**, 138758, 2024, https://doi.org/10.1016/j.molstruc.2024.138758

[3] R. Kaur, S. Chaudhary, K. Kumar, M.K. Gupta, and R.K. Rawal, "Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review", *European Journal of Medicinal Chemistry*, **132**, 108–134, 2017, https://doi.org/10.1016/j.ejmech.2017.03.025

[4] M. Najjar, M.A. Nasseri, M. Darroudi, and A. Allahresani, "Synthesis of dihydropyrimidinone and dihydropyridine derivatives by A GQDs-based magnetically nanocatalyst under solvent-free conditions", *Journal of Environmental Chemical Engineering*, **10**, 108854, 2022, https://doi.org/10.1016/j.jece.2022.108854

[5] G. Bosica, K. Demanuele, J.M. Padrón, and A. Puerta, "One-pot multicomponent green Hantzsch synthesis of 1,2-dihydropyridine derivatives with antiproliferative activity", *Beilstein Journal of Organic Chemistry*, **16**, 2862–2869, 2020, https://doi.org/10.3762/bjoc.16.235

[6] A. Chandravarkar, T. Aneeja, and G. Anilkumar, "Advances in Biginelli reaction: A comprehensive review", *Journal of Heterocyclic Chemistry*, 61, 5-28, 2024, https://doi.org/10.1002/jhet.4742

[7] P. Costanzo, M. Nardi, and M. Oliverio, "Similarity and competition between Biginelli and Hantzsch reactions: an opportunity for modern medicinal chemistry", *European Journal of Organic Chemistry*, **2020**, 3954–3964, 2020, https://doi.org/10.1002/ejoc.201901923

[8] G. Bosica, F. Cachia, R. De Nittis, and N. Mariotti, "Efficient one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones via a three-component Biginelli reaction", *Molecules*, **26**, 3753, 2021, https://doi.org/10.3390/molecules26123753

[9] Z. Mengting, X. Ying, Q. Yunan, P. Fen, L. Quan, and Z. Ming-Hua, "CuBr-promoted domino Biginelli reaction for the diastereoselective Synthesis of bridged polyheterocycles: Mechanism studies and in vitro anti-tumor activities", *Chinese Chemical Letters*, **33**, 4891–4895, 2022, https://doi.org/10.1016/j.cclet.2022.02.075

[10] L. Nana, Z. Jun, L. Tingting, Y. Hui, Ji. Mengna, L. Guang-Ning, L. Yunwu, D. Jianmin, Y. Fei, and W. Suna, "Two thiophene-functionalized Co-MOFs as green heterogeneous catalysts for the Biginelli reaction", *Inorganic Chemistry*, **63**(41), 19117-19129, 2024, https://doi.org/10.1021/acs.inorgchem.4c02497

[11] L. Yongsan, T. Tianhao, Z. Yuan, W. Yen, W. Dong, C. Rongjun, T. Lei, "Anticancer polymers via the Biginelli reaction", *ACS Macro Letters*, **9**, 1249–1254, 2020, https://doi.org/10.1021/acsmacrolett.0c00496

[12] R. Umer, S. Riffat, S. Nargis, H. Syed Fahad, Y. Farhana, A. Muhammad Jawad, I. Fatima, S. Nighat, A. Saba, Y. Masoom, A. Farzana Latif, and Q. Naveeda Akhter, "Structure based medicinal chemistry-driven strategy to design substituted dihydropyrimidines as

potential antileishmanial agents", *European Journal of Medicinal Chemistry*, **115**, 230–244, 2016, https://doi.org/10.1016/j.ejmech.2016.03.022

[13] P. Chen, and M. Tu, "Synthesis of 2-selenoxo DHPMs by Biginelli reaction with $Hf(OTf)_4$ as catalyst", *Tetrahedron Letters*, **59**, 987–990, 2018, https://doi.org/10.1016/j.tetlet.2018.01.070

[14] S. Farooq, F.A. Alharthi, A. Alsalme, A. Hussain, B.A. Dar, A. Hamid, and S. Koul, "Dihydropyrimidinones: Efficient one-pot green synthesis using montmorillonite-KSF and evaluation of their cytotoxic activity", *RSC Advances*, **10**, 42221–42234, 2020, https://doi.org/10.1039/D0RA09072G

[15] R. González-Olvera, V. Román-Rodríguez, G. Negrón-Silva, A. Espinoza-Vázquez, F. Rodríguez-Gómez, and R. Santillan, "Multicomponent synthesis and evaluation of new 1,2,3-triazole derivatives of dihydropyrimidinones as acidic corrosion inhibitors for steel", *Molecules*, **21**, 250, 2016, https://doi.org/10.3390/molecules21020250

[16] A. Mushtaq, A. Munawar, B. Parveen, S. Javed, A. F. Zahoor, K. G. Ali, A. Mansha and A. Irfan, "Recent advances in the synthesis of dihydropyrimidinones via Biginelli reaction", *Journal of the Iranian Chemical Society*, **21**, 2565-2586, 2024, https://doi.org/10.1007/s13738-024-03100-z

[17] S. Ghotekar, D. Sanap, K. Patel, Y. Abhale, A. Chauhan, L. Li, D. Kumar, K.-Y. A. Lin and R. Oza, "A bio-waste-mediated novel fabrication of $ZnCr_2O_4$ nanoparticles: a heterogeneous catalyst in Biginelli reaction", *Research on Chemical Intermediates*, **50**, 2199-219, 2024, https://doi.org/10.1007/s11164-024-05265-x

[18] G. Messire, E. Caillet, and S. Berteina-Raboin, "Green catalystsand/or green solvents for sustainable multi-component reactions", *Catalysts*, **14**(9), 593, 2024, https://doi.org/10.3390/catal14090593

[19] M. Marinescu, "Biginelli Reaction Mediated Synthesis of Antimicrobial Pyrimidine Derivatives and Their Therapeutic Properties", *Molecules*, **26**, 6022, 2021, https://doi.org/10.3390/molecules26196022

[20] T.K. Achar, A. Bose, and P. Mal, "Mechanochemical synthesis of small organic molecules", *Beilstein Journal of Organic Chemistry*, **13**, 1907–1931, 2017, https://doi.org/10.3762/bjoc.13.186

[21] M.S. Yusubov, and V.V. Zhdankin, "Iodine catalysis: A green alternative to transition metals in organic chemistry and technology", *Resource-Efficient Technologies*, **1**(1), 49–67, 2015, https://doi.org/10.1016/j.reffit.2015.06.001

[22] A. Dandia, S.L. Gupta, and S. Maheshwari, "Molecular iodine: Mild, green, and nontoxic lewis acid catalyst for the synthesis of heterocyclic compounds", *Green Chemistry: Synthesis of Bioactive Heterocycles*, 277–327, 2014, https://doi.org/10.1007/978-81-322-1850-0_10

[23] A.A.G.R.Y. Putra, P.O. Samirana, and D.A.A. Andhini, "Isolasi dan Karakterisasi Senyawa Flavonoid Potensial Antioksidan dari Daun Binahong (Anredera scandens (L.) Moq.)", *Jurnal Farmasi Udayana*, **90**, 2020, https://doi.org/10.24843/JFU.2019.v08.i02.p05

[24] Y. Ma, C. Qian, L. Wang, and M. Yang, "Lanthanide triflate catalyzed Biginelli reaction. One-pot synthesis of dihydropyrimidinons under solvent-free condition", *The Journal of Organic Chemistry*, **65**, 3864-3868, 2000, https://doi.org/10.1021/jo9919052