Research Article

Synthesis and Characterization of Novel Biginelli Dihydropyrimidinone Derivatives Containing Imidazole Moiety

Mashooq Ahmad Bhat ¹, Mohamed A. Al-Omar,¹ Ahmed M. Naglah ^{2,3},
Atef Kalmouch,³ and Abdullah Al-Dhfyani^{4,5}

¹Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

²Department of Pharmaceutical Chemistry, Drug Exploration and Development Chair (DEDC), College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

³Peptide Chemistry Department, Chemical Industries Research Division, National Research Centre, 12622 Dokki, Cairo, Egypt

⁴Stem Cell & Tissue Re-Engineering Program, Research Center, King Faisal Specialist Hospital and Research Center, MBC-03, P.O. Box 3354, Riyadh 11211, Saudi Arabia

⁵Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

Correspondence should be addressed to Mashooq Ahmad Bhat; mabhat@ksu.edu.sa

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Enaminone, (2*E*)-1-[4-(1*H*-imidazol-1-yl) phenyl]-4-methylpent-2-en-1-one (**II**) was synthesized by refluxing 1-[4-(1*H*-imidazol-1-yl) phenyl] ethan-1-one (**I**) with dimethylformamide dimethylacetal (DMF-DMA) under solvent-free condition for 12 hours. Finally, the dihydropyrimidinone derivatives containing imidazole moiety (**1–15**) were obtained by reacting enaminone, (2*E*)-1-[4-(1*H*-imidazol-1-yl) phenyl]-4-methylpent-2-en-1-one (**II**) with urea and different substituted benzaldehydes in the presence of glacial acetic acid. Dihydropyrimidinone derivatives containing imidazole moiety were synthesized in excellent yield by means of a simple and efficient method. All the compounds were confirmed by elemental analysis. The structures of all the compounds were confirmed by modern spectroscopic methods.

1. Introduction

Imidazole ring is an important five-membered aromatic pharmacophore, which is widely present in natural products and synthetic molecules. The special structural feature of imidazole ring with desirable electron-rich feature is beneficial for imidazole derivatives to readily bind with a variety of enzymes and receptors in biological environment to exhibit broad bioactivities. Numerous imidazole-based compounds as therapeutic drugs have been extensively used to treat various types of diseases. Many potent marketed drugs like ketoconazole, miconazole, clotrimazole, misonidazole, alpidem, flumazenil, metronidazole, luliconazole, dacarbazine, cimetidine, and clonidine contain imidazole moiety [1]. Imidazole-based compounds presents

various biological activities, such as anticancer, antifungal, antibacterial, antitubercular, anti-inflammatory, anti-neuropathic, antihypertensive, antihistaminic, antiparasitic, antiobesity, and antiviral [2]. A series of substituted aryloxy alkyl and aryloxy aryl alkyl imidazole were synthesized and evaluated *in vitro* as antileishmanial against *Leishmania donovani* [3]. Shingalapur et al. synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazoles derivatives and screened for *in vitro* antitubercular activity against *Mycobacterium tuberculosis* [4]. Puratchikody and Doble studied on 2-substituted-4,5-diphenyl-1*H*-imidazoles and checked the anti-inflammatory activity based on the Carrageenan-induced paw edema method [5]. Sharma et al. have synthesized 2-(substituted phenyl)-1*H*-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-

yl]-menthanone analogues and screened for antimicrobial activity against Gram-positive, Gram-negative, and fungal species [6].

Pyrimidines have played an important role in the medicinal chemistry [7]. Pyrimidines are important scaffold in the field of medicinal chemistry because of their potential biological activities such as antitumor, antiviral, and antibacterial agents [8]. 4-Aryl-1,4-dihydropyrimidines like nifedipine was first introduced as antihypertensive into clinical medicine in 1975. Dihydropyrimidines are the most potent calcium-channel modulators available for the treatment of various cardiovascular diseases.

Substituted dihydropyrimidinone compounds show interesting biological properties. Dihydropyrimidinones have emerged as the integral back bone of calcium-channel blockers [9] and antihypertensive agents [10]. These compounds exhibit a broad range of biological activities such as antiviral, antitumor, antibacterial, and anti-inflammatory [11]. Dihydropyrimidinone compounds were first synthesized by Pietro Biginelli. The type of compounds was known as Biginelli compounds. The process comprised numerous reacting aldehydes with urea and a beta-keto ester to give a tetrahydropyrimidinone [12–14]. Dihydropyrimidines are associated with a broad spectrum of biological activities [15].

The literature study suggested that compounds containing these two important scaffolds (imidazole and dihydropyrimidinone) may have significant therapeutic potential. In the present disclosure, a series of novel imidazole dihydropyrimidinone hybrids were synthesized and characterized by spectral data and elemental analysis.

2. Experimental

2.1. Chemistry. Solvents were procured from Merck. Thin layer chromatography (TLC) was performed on Silica gel 60 F₂₅₄-coated plates (Merck) to check the purity of compounds. For performing FTIR, Perkin Elmer FT-IR spectrophotometer was used. Melting points were determined using Gallenkamp melting point apparatus. ¹H and ¹³C NMR were recorded in Bruker NMR 500/700 MHz and 125/176 MHz spectrophotometer. The samples were run in DMSO-*d*₆ with tetra methyl silane (TMS) as an internal standard. Molecular masses of compounds were determined by mass spectroscopy. The CHN (Elementar Analysensysteme GmbH, Germany) was used for elemental analysis of the compounds.

2.2. Synthesis of (2*E*)-1-[4-(1*H*-imidazol-1-yl) phenyl]-4-methylpent-2-en-1-one. A mixture of 1-[4-(1*H*-imidazol-1-yl)phenyl]ethan-1-one (**I**) (0.02 mol) and dimethyl formamide-dimethylacetal (DMF-DMA) (**II**) (0.023 mol) was refluxed for 12 h under solvent-free condition on a heating mantle, then the mixture was left to cool slowly at room temperature. The precipitate was obtained. Diethyl ether was added to the precipitate, and filtration was performed under vacuum. The obtained product was recrystallized from absolute ethanol.

2.3. General Synthesis of 5-[4-(1*H*-imidazol-1-yl) benzoyl]-4-(substituted phenyl)-3,4-dihydropyrimidin-2(1*H*)-one (1–15**).** A mixture of enaminone, (2*E*)-1-[4-(1*H*-imidazol-1-yl) phenyl]-4-methylpent-2-en-1-one (0.01 mol), different substituted benzaldehydes (0.01 mol), urea (0.01 mol), and glacial acetic acid (10 mL) was refluxed for 3 hours. The precipitates (**1–15**) were obtained by pouring the reaction mixture into the cold water (50 mL). The products were obtained by filtration under vacuum. The products were washed several times with cold water. The obtained products were recrystallized from glacial acetic acid (5 mL) and ethanol (100 mL) mixture. In the ¹H-NMR spectra, the signals of the individual protons of the compounds were verified on the basis of multiplicity, chemical shifts, and coupling constant. Analytical and spectral data for the compounds were in good agreement with the expected structures of the compounds.

2.3.1. 5-[4-(1*H*-imidazol-1-yl)benzoyl]-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (1**).** Yield: 75%; m.p.: 130–132°C; IR (KBr) cm^{−1}: 3110 (NH str.), 1700 (C=O), 1601 (C=O), 1476 (C=C), 1214 (C-O); ¹H NMR (500 MHz, DMSO-*d*₆): δ = 6.12 (1H, d, *J* = 2.5 Hz, C-4), 7.14 (1H, s, imidazole H), 7.53 (1H, s, imidazole H), 7.54–7.94 (9H, m, Ar-H), 7.95 (1H, s, imidazole H), 8.30 (1H, s, NH, D₂O exchg.) 8.49 (1H, s, =CH), 9.66 (1H, s, NH, D₂O exchg.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 56.4, 60.7, 116.6, 118.2, 120.1, 124.5, 130.0, 130.4, 130.6, 132.4, 134.4, 136.1, 136.6, 138.6, 143.0, 148.3, 150.8, 153.2, 190.6; MS: *m/z* = 345.03 [M+1]⁺; Analysis: for C₂₀H₁₆N₄O₂, calcd. C 69.76, H 4.68, N 16.27%; found C 69.96, H 4.69, N 16.31%.

2.3.2. 5-[4-(1*H*-imidazol-1-yl)benzoyl]-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (2**).** Yield: 80%; m.p.: 155–157°C; IR (KBr) cm^{−1}: 3109 (NH str.), 1700 (C=O), 1599 (C=O), 1516 (C=C), 1245 (C-O); ¹H NMR (500 MHz, DMSO-*d*₆): δ = 5.61 (1H, s, C-4), 7.14 (1H, s, imidazole H), 7.20 (1H, s, imidazole H), 7.66–7.84 (8H, m, Ar-H), 7.93 (1H, s, imidazole H), 8.23 (1H, s, NH, D₂O exchg.) 8.37 (1H, s, =CH), 9.67 (1H, s, NH, D₂O exchg.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 53.0, 56.2, 111.3, 118.0, 120.1, 123.5, 124.0, 128.2, 129.5, 130.1, 130.5, 130.4, 136.0, 136.5, 139.0, 143.0, 147.1, 151.2, 151.2, 190.6; MS: *m/z* = 389.58 [M]⁺; Analysis: for C₂₀H₁₅N₅O₄, calcd. C 61.69, H 3.88, N 17.99%; found C 61.87, H 3.89, N 17.95%.

2.3.3. 5-[4-(1*H*-imidazol-1-yl)benzoyl]-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (3**).** Yield: 80%; m.p.: 158–160°C; IR (KBr) cm^{−1}: 3107 (NH str.), 1700 (C=O), 1599 (C=O), 1512 (C=C), 1181 (C-O); ¹H NMR (500 MHz, DMSO-*d*₆): δ = 5.61 (1H, s, C-4), 7.14 (1H, s, imidazole H), 7.20 (1H, s, imidazole H), 7.66–7.84 (8H, m, Ar-H), 7.93 (1H, s, imidazole H), 8.23 (1H, s, NH, D₂O exchg.) 8.37 (1H, s, =CH), 9.67 (1H, s, NH, D₂O exchg.); ¹³C NMR (125.76 MHz, DMSO-*d*₆): δ = 53.7, 56.5, 111.7, 118.3, 120.2, 123.9, 124.3, 128.4, 129.6, 130.4, 130.7, 130.9, 136.1, 136.8, 139.2, 143.0, 147.2, 151.3, 151.5, 190.7;

MS: $m/z = 390.17$ $[M+1]^+$; Analysis: for $C_{20}H_{15}N_5O_4$, calcd. C 61.69, H 3.88, N 17.99%; found C 61.51, H 3.87, N 17.96%.

2.3.4. 5-[4-(1H-imidazol-1-yl)benzoyl]-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**4**). Yield: 82%; m.p.: 160–162°C; IR (KBr) cm^{-1} : 3447 (NH str.), 1700 (C=O), 1654 (C=O), 1609 (C=C), 1057 (C-O); ^1H NMR (500 MHz, DMSO- d_6): $\delta = 5.64$ (1H, s, C-4), 7.14 (1H, s, imidazole H), 7.25 (1H, s, imidazole H), 7.62–7.87 (8H, m, Ar-H), 7.87 (1H, s, imidazole H), 8.22 (1H, s, NH, D_2O exchg.) 8.37 (1H, s, =CH), 9.71 (1H, s, NH, D_2O exchg.); ^{13}C NMR (125.76 MHz, DMSO- d_6): $\delta = 53.6, 56.5, 111.7, 115.8, 118.3, 120.2, 121.8, 122.7, 122.9, 130.1, 130.4, 130.6, 130.7, 133.8, 136.1, 136.8, 137.5, 139.1, 139.2, 140.7, 143.2, 146.5, 148.2, 151.4, 190.8$; MS: $m/z = 390.11$ $[M+1]^+$; Analysis: for $C_{20}H_{15}N_5O_4$, calcd. C 61.69, H 3.88, N 17.99%; found C 61.58, H 3.86, N 17.97%.

2.3.5. 4-(4-chlorophenyl)-5-[4-(1H-imidazol-1-yl)benzoyl]-3,4-dihydropyrimidin-2(1H)-one (**5**). Yield: 90%; m.p.: 180–182°C; IR (KBr) cm^{-1} : 3410 (NH str.), 1700 (C=O), 1654 (C=O), 1604 (C=C), 1055 (C-O); ^1H NMR (500 MHz, DMSO- d_6): $\delta = 5.46$ (1H, s, C-4), 7.13 (1H, s, imidazole H), 7.15 (1H, s, imidazole H), 7.39–7.76 (8H, m, Ar-H), 7.84 (1H, s, imidazole H), 7.96 (1H, s, NH, D_2O exchg.) 8.37 (1H, s, =CH), 9.53 (1H, s, NH, D_2O exchg.); ^{13}C NMR (125.76 MHz, DMSO- d_6): $\delta = 53.4, 56.5, 112.3, 116.3, 118.3, 120.2, 128.5, 130.1, 130.3, 130.7, 131.1, 132.4, 136.0, 136.1, 137.0, 137.7, 139.0, 139.1, 140.0, 142.6, 143.4, 151.5, 190.8$; MS: $m/z = 378.77$ $[M]^+$; Analysis: for $C_{20}H_{15}ClN_4O_2$, calcd. C 63.41, H 3.99, N 14.79%; found C 63.60, H 4.00, N 14.83%.

2.3.6. 4-(2,4-dichlorophenyl)-5-[4-(1H-imidazol-1-yl)benzoyl]-3,4-dihydropyrimidin-2(1H)-one (**6**). Yield: 87%; m.p.: 138–140°C; IR (KBr) cm^{-1} : 3111 (NH str.), 1700 (C=O), 1604 (C=O), 1618 (C=C), 1216 (C-O); ^1H NMR (500 MHz, DMSO- d_6): $\delta = 5.86$ (1H, s, C-4), 7.16 (1H, s, imidazole H), 7.19 (1H, s, imidazole H), 7.53–7.77 (7H, m, Ar-H), 7.84 (1H, s, imidazole H), 7.93 (1H, s, NH, D_2O exchg.) 8.39 (1H, s, =CH), 9.63 (1H, s, NH, D_2O exchg.); ^{13}C NMR (125.76 MHz, DMSO- d_6): $\delta = 56.5, 110.9, 118.3, 120.2, 120.4, 128.2, 129.4, 130.4, 130.6, 131.5, 133.2, 133.6, 136.1, 136.8, 139.2, 140.1, 143.1, 150.9, 170.0, 172.1, 190.5$; MS: $m/z = 414.30$ $[M+1]^+$; Analysis: for $C_{20}H_{14}Cl_2N_4O_2$, calcd. C 58.13, H 3.41, N 13.56%; found C 58.30, H 3.40, N 13.52%.

2.3.7. 5-[4-(1H-imidazol-1-yl)benzoyl]-4-(2-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**7**). Yield: 77%; m.p.: 140–142°C; IR (KBr) cm^{-1} : 3136 (NH str.), 1700 (C=O), 1690 (C=O), 1618 (C=C), 1111 (C-O); ^1H NMR (500 MHz, DMSO- d_6): $\delta = 3.78$ (3H, s, OCH_3), 5.75 (1H, s, C-4), 6.92 (1H, s, imidazole H), 7.10 (1H, s, imidazole H), 7.25–7.77 (8H, m, Ar-H), 7.84 (1H, s, imidazole H), 7.87 (1H, s, NH, D_2O exchg.) 8.40 (1H, s, =CH), 9.44 (1H, s, NH, D_2O exchg.); ^{13}C NMR (125.76 MHz, DMSO- d_6): $\delta = 49.6, 55.7, 111.3, 111.8, 112.0, 112.7, 118.3, 120.2, 120.3, 120.5, 120.7,$

130.3, 130.7, 136.1, 137.2, 139.0, 142.83, 151.9, 157.3, 190.7, 193.1; MS: $m/z = 375.08$ $[M+1]^+$; Analysis: for $C_{21}H_{18}N_4O_3$, calcd. C 67.37, H 4.85, N 14.96%; found C 67.57, H 4.86, N 14.92%.

2.3.8. 4-(4-hydroxyphenyl)-5-[4-(1H-imidazol-1-yl)benzoyl]-3,4-dihydropyrimidin-2(1H)-one (**8**). Yield: 65%; m.p.: 2102–12°C; IR (KBr) cm^{-1} : 3411 (NH str.), 1700 (C=O), 1654 (C=O), 1619 (C=C), 1056 (C-O); ^1H NMR (500 MHz, DMSO- d_6): $\delta = 6.10$ (1H, d, $J = 2.5$ Hz, C-4), 7.14 (1H, s, imidazole H), 7.53 (1H, s, imidazole H), 7.54–7.94 (8H, m, Ar-H), 7.95 (1H, s, imidazole H), 8.30 (1H, s, NH, D_2O exchg.) 8.49 (1H, s, =CH), 9.66 (1H, s, NH, D_2O exchg.) 10.2 (1H, s, NH, D_2O exchg.); MS: $m/z = 361.44$ $[M+1]^+$; Analysis: for $C_{20}H_{16}N_4O_3$, calcd. C 66.66, H 4.48, N 15.55%; found C 66.46, H 4.47, N 15.51%.

2.3.9. 4-(3-hydroxyphenyl)-5-[4-(1H-imidazol-1-yl)benzoyl]-3,4-dihydropyrimidin-2(1H)-one (**9**). Yield: 66%; m.p.: 190–192°C; IR (KBr) cm^{-1} : 3421 (NH str.), 1717 (C=O), 1684 (C=O), 1600 (C=C), 1055 (C-O); ^1H NMR (500 MHz, DMSO- d_6): $\delta = 5.46$ (1H, d, $J = 2.5$ Hz, C-4), 7.13 (1H, s, imidazole H), 7.50 (1H, s, imidazole H), 7.52–7.90 (8H, m, Ar-H), 7.95 (1H, s, imidazole H), 8.30 (1H, s, NH, D_2O exchg.) 8.49 (1H, s, =CH), 9.66 (1H, s, NH, D_2O exchg.) 10.2 (1H, s, NH, D_2O exchg.); MS: $m/z = 360.98$ $[M]^+$; Analysis: for $C_{20}H_{16}N_4O_3$, calcd. C 66.66, H 4.48, N 15.55%; found C 66.48, H 4.46, N 15.52%.

2.3.10. 5-[4-(1H-imidazol-1-yl)benzoyl]-4-(3-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**10**). Yield: 68%; m.p.: 125–127°C; IR (KBr) cm^{-1} : 3125 (NH str.), 1700 (C=O), 1602 (C=O), 1418 (C=C), 1248 (C-O); ^1H NMR (500 MHz, DMSO- d_6): $\delta = 3.75$ (3H, s, OCH_3), 5.46 (1H, s, C-4), 6.92 (1H, s, imidazole H), 6.97 (1H, s, imidazole H), 7.16–7.66 (8H, m, Ar-H), 7.76 (1H, s, imidazole H), 7.83 (1H, s, NH, D_2O exchg.) 8.41 (1H, s, =CH), 9.51 (1H, s, NH, D_2O exchg.); ^{13}C NMR (125.76 MHz, DMSO- d_6): $\delta = 53.7, 55.3, 112.6, 112.9, 113.0, 116.6, 118.3, 118.9, 120.2, 120.3, 120.4, 120.5, 130.2, 130.3, 130.9, 136.1, 137.1, 137.8, 139.0, 139.1, 141.3, 142.4, 145.9, 151.8, 159.7, 190.8, 193.1$; MS: $m/z = 374.55$ $[M]^+$; Analysis: for $C_{21}H_{18}N_4O_3$, calcd. C 67.37, H 4.85, N 14.96%; found C 67.58, H 4.87, N 14.93%.

2.3.11. 5-[4-(1H-imidazol-1-yl)benzoyl]-4-(2,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**11**). Yield: 70%; m.p.: 135–137°C; IR (KBr) cm^{-1} : 3421 (NH str.), 1700 (C=O), 1654 (C=O), 1604 (C=C), 1206 (C-O); ^1H NMR (500 MHz, DMSO- d_6): $\delta = 3.75$ (9H, s, $3 \times OCH_3$), 5.60 (1H, s, C-4), 6.75 (1H, s, imidazole H), 6.90 (1H, s, imidazole H), 7.15–7.60 (6H, m, Ar-H), 7.75 (1H, s, imidazole H), 7.83 (1H, s, NH, D_2O exchg.) 8.38 (1H, s, =CH), 9.39 (1H, s, NH, D_2O exchg.); MS: $m/z = 434.80$ $[M]^+$; Analysis: for $C_{23}H_{22}N_4O_5$, calcd. C 63.59, H 5.10, N 12.90%; found C 63.40, H 5.11, N 12.86%.

Compd.	R
1	C ₆ H ₅
2	2-NO ₂ -C ₆ H ₄
3	4-NO ₂ -C ₆ H ₄
4	3-NO ₂ -C ₆ H ₄
5	4-Cl-C ₆ H ₄
6	2,4-(Cl) ₂ -C ₆ H ₃
7	2-OCH ₃ -C ₆ H ₄
8	4-OH-C ₆ H ₄
9	3-OH-C ₆ H ₄
10	3-OCH ₃ -C ₆ H ₄
11	2,4,5-(OCH ₃) ₃ -C ₆ H ₂
12	2,3,4-(OCH ₃) ₃ -C ₆ H ₂
13	3,4,5-(OCH ₃) ₃ -C ₆ H ₂
14	2,4,6-(OCH ₃) ₃ -C ₆ H ₂
15	3,4-(OCH ₃) ₂ -C ₆ H ₃

SCHEME 1: Reaction scheme for the synthesis of dihydropyrimidinone derivatives containing imidazole moiety.

2.3.12. 5-[4-(1H-imidazol-1-yl)benzoyl]-4-(2,3,4-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**12**). Yield: 72%; m.p.: 138–140°C; IR (KBr) cm⁻¹: 3412 (NH str.), 1718 (C=O), 1654 (C=O), 1618 (C=C), 1248 (C-O); ¹H NMR (500 MHz, DMSO-d₆): δ = 3.78 (9H, s, 3 × OCH₃), 5.45 (1H, s, C-4), 6.67 (1H, s, imidazole H), 6.70 (1H, s, imidazole H), 7.70–7.78 (6H, m, Ar-H), 7.85 (1H, s, imidazole H), 7.91 (1H, s, NH, D₂O exchg.) 8.39 (1H, s, =CH), 9.49 (1H, s, NH, D₂O exchg.); ¹³C NMR (125.76 MHz, DMSO-d₆): δ = 53.8, 56.3, 60.4, 60.6, 104.1, 105.2, 105.4, 106.1, 118.3, 120.3, 130.7, 131.0, 136.1, 137.1, 137.2, 138.0, 139.2, 139.8, 140.3, 142.7, 151.6, 153.3, 153.5, 191.0; MS: *m/z* = 435.00 [M+1]⁺; Analysis: for C₂₃H₂₂N₄O₅, calcd. C 63.59, H 5.10, N 12.90%; found C 63.48, H 5.12, N 12.85%.

2.3.13. 5-[4-(1H-imidazol-1-yl)benzoyl]-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**13**).

Yield: 75%; m.p.: 128–130°C; IR (KBr) cm⁻¹: 3117 (NH str.), 1700 (C=O), 1654 (C=O), 1604 (C=C), 1245 (C-O); ¹H NMR (500 MHz, DMSO-d₆): δ = 3.75 (9H, s, 3 × OCH₃), 5.62 (1H, s, C-4), 6.76 (1H, s, imidazole H), 7.00 (1H, s, imidazole H), 7.16–7.61 (6H, m, Ar-H), 7.75 (1H, s, imidazole H), 7.83 (1H, s, NH, D₂O exchg.) 8.38 (1H, s, =CH), 9.39 (1H, s, NH, D₂O exchg.); ¹³C NMR (125.76 MHz, DMSO-d₆): δ = 49.8, 56.2, 56.5, 60.6, 61.1, 61.3, 80.0, 112.3, 118.3, 120.3, 123.1, 129.7, 130.3, 130.7, 136.2, 137.2, 138.0, 139.0, 139.5, 142.0, 142.3, 151.6, 152.2, 153.4, 190.7; MS: *m/z* = 434.00 [M]⁺; Analysis: for C₂₃H₂₂N₄O₅, calcd. C 63.59, H 5.10, N 12.90%; found C 63.50, H 5.09, N 12.89%.

2.3.14. 5-[4-(1H-imidazol-1-yl)benzoyl]-4-(2,4,6-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**14**). Yield: 74%; m.p.: 130–132°C; IR (KBr) cm⁻¹: 3421 (NH str.), 1718 (C=O), 1654 (C=O), 1618 (C=C), 1149 (C-O); ¹H NMR

SCHEME 2: Possible mechanism of the reaction for the synthesis of dihydropyrimidinone derivatives containing imidazole moiety (1-15).

(500 MHz, $\text{DMSO}-d_6$): δ = 3.75 (9H, s, $3 \times \text{OCH}_3$), 5.61 (1H, s, C-4), 6.75 (1H, s, *imidazole H*), 7.10 (1H, s, *imidazole H*), 7.18–7.62 (6H, *m*, Ar-H), 7.72 (1H, s, *imidazole H*), 7.83 (1H, s, NH, D_2O exchg.) 8.38 (1H, s, =CH), 9.40 (1H, s, NH, D_2O exchg.); MS: m/z = 434.60 $[\text{M}]^+$; Analysis: for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_5$, calcd. C 63.59, H 5.10, N 12.90%; found C 63.55, H 5.08, N 12.84%.

2.3.15. 5-[4-(1*H*-imidazol-1-yl)benzoyl]-4-(3,4-dimethoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (15). Yield: 75%; m.p.: 136–138°C; IR (KBr) cm^{-1} : 3117 (NH str.), 1700 (C=O), 1654 (C=O), 1618 (C=C), 1138 (C-O); ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 3.76 (6H, s, $3 \times \text{OCH}_3$), 5.45 (1H, s, C-4), 6.90 (1H, s, *imidazole H*), 7.18 (1H, s, *imidazole H*), 7.63–7.80 (7H, *m*, Ar-H), 7.84 (1H, s, *imidazole H*), 7.90 (1H, s, NH, D_2O exchg.) 8.38 (1H, s, =CH), 9.48 (1H, s, NH, D_2O exchg.); ^{13}C NMR (125.76 MHz, $\text{DMSO}-d_6$): δ = 53.4, 55.8, 55.9, 56.5, 110.9, 112.1, 112.7, 118.3, 118.7, 120.2, 120.3, 130.3, 136.1, 136.8, 137.2, 139.0, 139.1, 139.4, 142.2, 148.6, 149.0, 151.7, 190.9, 193.3; MS: m/z = 404.21 $[\text{M}]^+$; Analysis:

for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_4$, calcd. C 65.34, H 4.98, N 13.85%; found C 63.14, H 4.99, N 13.81%.

3. Results and Discussion

As shown in Scheme 1, enaminone, (2*E*)-1-[4-(1*H*-imidazol-1-yl) phenyl]-4-methylpent-2-en-1-one (II) was synthesized by refluxing 1-[4-(1*H*-imidazol-1-yl) phenyl] ethan-1-one (I) with dimethylformamide dimethylacetal (DMF-DMA) under solvent-free conditions for 12 hours. To prepare the final dihydropyrimidinone derivatives, a mixture of substituted benzaldehyde (0.01 mol) III, enaminone (II) (0.01 mol), urea (0.01 mol) IV, and glacial acetic acid (10 mL) was heated under reflux for 3 hours. The precipitates of compounds (1-15) were collected by vacuum filtration. The product was washed several times with water and recrystallized from glacial acetic acid and ethanol mixture. ^1H NMR spectrum of (II) displayed two singlets at δ H 2.89, 3.12 ppm due to the N, N-dimethyl protons and two doublets at δ H 5.80–5.82 and 7.63–7.65 ppm (d, J = 14 Hz) due to the ethylenic protons, in addition to the two doublets at the

region δ H 7.0 ppm (2H, d, aromatic) and δ H 7.82 ppm (2H, d, aromatic). The value of coupling constant ($J = 14$ Hz) for the ethylenic protons indicates that the enaminones existed in the *e*-configuration which was also confirmed by single-crystal X-ray crystallography [16].

All of the compounds presented the D₂O exchangeable broad singlet at δ H 7.83–8.30 ppm and δ H 9.39–9.71 ppm corresponding to the two NH protons. The H-4 and =CH protons of dihydropyrimidinone moiety were observed at δ H 5.45–6.12 and 8.37–8.49 ppm, respectively [17–19]. The presence of all carbon atoms for compounds was confirmed by ¹³C NMR spectra. Molecular weight of compounds was confirmed by mass spectra. All the compounds gave molecular ion peak respective to their molecular weights. The detailed spectral results of ¹H NMR, ¹³C NMR spectra and mass spectra are given in the experimental part. The spectral and analytical data confirmed the composition of the synthesized compounds (1–15).

The possible reaction mechanism for dihydropyrimidinone derivative containing imidazole (1–15) involves the acid-catalyzed formation of iminium ion intermediate from the substituted aryl aldehydes and urea. Reaction of iminium ion by enaminone of imidazole produces ureidenone, which cyclizes to form hexahydropyrimidine. Elimination of N(CH₃)₂ group from hexahydropyrimidine in presence of glacial acetic acid produces final dihydropyrimidinone derivative (1–15) containing imidazole moiety (Scheme 2).

4. Conclusion

In conclusion, novel Biginelli dihydropyrimidinone derivatives containing imidazole moiety (1–15) were synthesized efficiently in good yield with a simple method, consisting of three components in a single pot. The starting material enaminone was synthesized by reacting imidazole acetophenone with dimethylformamide dimethylacetal (DMF-DMA) under solvent-free condition. Novel dihydropyrimidinone derivatives were obtained by reacting enaminone with different substituted benzaldehydes and urea in presence of glacial acetic acid. All the novel synthesized compounds were fully characterized by spectral data and elemental analysis.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request. Samples of the compounds (1–15) in pure form are available from authors.

Conflicts of Interest

The authors declare no conflicts of interest.

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