Research Article

Biginelli Synthesis of Novel Dihydropyrimidinone Derivatives Containing Phthalimide Moiety

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A new series of novel Biginelli compounds, 5-benzoyl-substituted phenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (1–10), were synthesized from enaminone, 2-{4-[(2E)-3-(dimethylamino)prop-2-enoyl]phenyl}-1H-isoindole-1,3(2H)-dione (IV), which was synthesized by refluxing 2-(4-acetylphenyl)-1H-isoindole-1,3(2H)-dione (III) with dimethylformamide-dimethylacetal (DMF-DMA) without solvent for 12 h. The compound 2-(4-acetylphenyl)-1H-isoindole-1,3(2H)-dione (III) was obtained by reacting phthalic anhydride (I) with para-aminoacetophenone (II) in glacial acetic acid for 2 h. The dihydropyrimidinone derivatives containing phthalimide moiety (1–10) were obtained by reacting enaminone, 2-[(2E)-3-(dimethylamino)prop-2-enoyl] phenyl-1H-isoindole-1,3(2H)-dione (IV), with urea and different substituted benzaldehydes in the presence of glacial acetic acid for 3 h. Simple and efficient method was employed to synthesize the dihydropyrimidinone derivatives containing phthalimide moiety. Structures of all the synthesized compounds were characterized by spectroscopic methods.

1. Introduction

Pyrimidines have played a vital role in the field of pharmaceutical chemistry [1]. Pyrimidines are important moieties because of their various pharmacological activities. Nifedipine, 4-aryl-1,4-dihydropyridines, was the first antihyperensive agent into the clinical medicine. For the treatment of various cardiovascular diseases, dihydropyridines are the most potent calcium channel modulators [2, 3].

Substituted dihydropyrimidinone compounds show interesting biological properties, e.g., calcium channel blockers and antihypertensive agents [4, 5]. These compounds display a broad spectrum of biological activities such as anti-inflammatory, antitumor, antiviral, and antibacterial ones [6, 7]. Dihydropyrimidinone compounds were first synthesized by Pietro Biginelli. The type of compounds is known as Biginelli compounds. The synthesis of this type of compounds involves the reacting of numerous aldehydes with urea and a beta-keto ester to give a tetrahydropyrimidinone.

Phthalimide analogues have been reported with large range of pharmacological activities that are anticonvulsant, anti-inflammatory, analgesic, and hypolipidemic [8–11]. Phthalimide analogues have been synthesized as tumor necrosis factor-α (TNF-α) inhibitors [12]. TNF-α plays an important role in certain physiological immune systems. It stimulates the inflammatory response leading to autoimmune disorders including rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis, psoriasis, and refractory asthma [13]. Extensive research on the phthalimide analogues has been reported in the literature [14–17].

The hybrid compounds containing these two important moieties (dihydropyrimidinone and phthalimide) may have
2. Experiment

2.1. Chemistry.

Solvents were procured from Merck, New Jersey, USA. Thin layer chromatography (TLC) was performed on Silica gel 60 F254 coated plates (Merck, Millipore, Billerica, MA, USA). The reaction mixture was added to the ice cold water. The samples were dissolved in DMSO-d6 with tetramethylsilane (TMS) as an internal standard. The molecular masses of compounds were determined by Agilent triple quadrupole 6410 TQ GC/MS equipped with ESI (electrospray ionization) source (5301 Stevens Creek Blvd, Santa Clara, CA 95051, USA). The CHN elemental analyses were performed on a Carlo Erba elemental analyzer (Elementar Analysensysteme GmbH, Langenselbold, Germany) using a CE-440 elemental analyzer. The CHN results were supported by MS: 468.41 [M]+; Analysis: for C25H16N4O6 calcd. C 64.10, H 3.44, N 11.96%; Found C 64.26, H 3.43, N 11.97%.

2.2. Synthesis of the Dihydropyrimidine Derivatives (I-10).

A mixture of enamino, 2,4-dimethoxy and 2,4-dimethoxyphenyl-1H-isoindole-1,3(2H)-dione (IV), was recrystallized from absolute ethanol.

2.2.1. 5-Benzoyl-3,4-dimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (I). m.p.: 190–192°C; 1H NMR (500 MHz, DMSO-d6): δ = 3.81 (3H, s, -OCH3), 3.89 (3H, s, OCH3), 5.76 (1H, s, H-4), 6.94–7.99 (12H, m, Ar-H), 9.36 (1H, s, CONH, D2O exchg.), 10.31 (1H, s, NH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): δ = 49.8, 56.5, 60.6, 62.4, 65.4, 112.3, 112.6, 118.7, 120.2, 123.9, 124.4, 127.4, 129.0, 131.9, 134.4, 135.2, 137.3, 138.4, 146.6, 146.6, 151.4, 152.9, 167.2, 190.4, 191.1; MS: m/z = 483.47 [M]+; Analysis: for C25H18N3O4 calculated C 67.07, H 4.38, N 8.69%; Found C 67.27, H 4.37, N 8.67%.

2.2.2. 5-Benzoyl-4-nitrophenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (2). m.p.: 175–177°C; 1H NMR (500 MHz, DMSO-d6): δ = 5.62 (1H, s, H-4), 7.20–8.41 (13H, m, Ar-H), 9.60 (1H, s, CONH, D2O exchg.), 10.16 (1H, s, NH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): δ = 111.7, 123.1, 124.6, 128.4, 129.1, 131.0, 131.9, 134.6, 135.2, 138.0, 140.5, 143.3, 147.2, 151.5, 167.2, 191.1, 192.7, 207.0; MS: m/z = 468.41 [M]+; Analysis: for C25H18N3O4 calculated C 67.26, H 4.39, N 8.71%.

2.2.3. 5-Benzoyl-4-nitrophenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (3). m.p.: 240–242°C; 1H NMR (500 MHz, DMSO-d6): δ = 5.64 (1H, s, H-4), 7.22–8.22 (13H, m, Ar-H), 9.60 (1H, s, CONH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): δ = 111.6, 121.7, 123.0, 124.0, 127.4, 129.4, 131.0, 133.7, 134.6, 135.2, 138.0, 145.3, 147.2, 151.5, 167.2, 191.1, 192.7, 207.0; MS: m/z = 468.41 [M]+; Analysis: for C25H16N4O6 calculated C 67.61, H 4.34 N 11.96%; Found C 67.24, H 3.45, N 11.98%.

2.2.4. 5-Benzoyl-2,4,5-trimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (4). m.p.: 170–172°C; 1H NMR (500 MHz, DMSO-d6): δ = 6.17 (1H, s, H-4), 7.22–7.98 (13H, m, Ar-H), 9.62 (1H, s, CONH, D2O exchg.), 10.30 (1H, s, NH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): δ = 111.6, 123.9, 124.5, 127.3, 129.3, 130.0, 131.9, 134.5, 135.2, 137.7, 138.5, 143.3, 148.3, 151.3, 167.2, 191.2; MS: m/z = 468.41 [M]+; Analysis: for C25H16N4O6 calculated C 67.61, H 4.34 N 11.96%; Found C 67.24, H 3.46, N 11.94%.

2.2.5. 5-Benzoyl-2,3-dimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (5). m.p.: 190–192°C; 1H NMR (500 MHz, DMSO-d6): δ = 3.81 (3H, s, -OCH3), 3.89 (3H, s, OCH3), 5.76 (1H, s, H-4), 6.94–7.99 (12H, m, Ar-H), 9.36 (1H, s, CONH, D2O exchg.), 10.31 (1H, s, NH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): δ = 49.8, 56.5, 60.6, 62.4, 65.4, 112.3, 112.6, 118.7, 120.2, 123.9, 124.4, 127.4, 129.0, 131.9, 134.4, 135.2, 137.3, 138.4, 146.6, 146.6, 151.4, 152.9, 167.2, 190.4, 191.1; MS: m/z = 483.47 [M]+; Analysis: for C25H18N3O4 calculated C 67.07, H 4.38, N 8.69%; Found C 67.26, H 4.39, N 8.71%.

2.2.6. 5-Benzoyl-2,4,5-trimethoxyphenyl-3,4-dihydropyrimidin-2(1H)-one-1H-isoindole-1,3(2H)-dione (6). m.p.: 180–182°C; 1H NMR (500 MHz, DMSO-d6): δ = 3.69 (3H, s, OCH3), 3.79 (3H, s, OCH3), 3.84 (3H, s, OCH3), 5.60 (1H, s, H-4), 6.73–8.00.
(11H, m, Ar-H), 9.33 (1H, s, CONH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): \( \delta \) 49.5, 56.2, 56.5, 56.9, 65.4, 99.2, 111.5, 113.1, 123.0, 124.0, 127.5, 129.0, 131.0, 134.4, 135.2, 135.4, 138.5, 142.8, 149.7, 151.7, 152.0, 167.2, 191.6; MS: m/z 513.49 [M]+; Analysis: for C28H23N3O7 calcd. C 65.49, H 4.51, N 8.18%; Found C 65.47, H 4.50, N 8.20%.

2.2.7. 5-Benzoyl-3,4,5-trimethoxyphenyl-3,4-dihydropyrimidine-2(1H)-one-1H-isoindole-1,3(2H)-dione (7). m.p.: 195–197°C; 1H NMR (500 MHz, DMSO-d6): \( \delta \) 3.66 (3H, s, -OCH3), 3.79 (6H, s, OCH3), 5.45 (1H, s, H-4), 6.67–7.99 (11H, m, Ar-H), 9.44 (1H, s, CONH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): \( \delta \) 53.7, 56.3, 56.5, 60.4, 65.4, 104.0, 112.1, 124.0, 127.5, 129.1, 131.9, 134.5, 135.2, 137.2, 138.3, 139.8, 151.5, 153.3, 167.2, 191.3; MS: m/z = 513.49 [M]+; Analysis: for C29H23N2O7 calcd. C 65.49, H 4.51, N 8.18%; Found C 65.46, H 4.52, N 8.16%.

2.2.8. 5-Benzoyl-2,3,4-trimethoxyphenyl-3,4-dihydropyrimidine-2(1H)-one-1H-isoindole-1,3(2H)-dione (8). m.p.: 168–170°C; 1H NMR (500 MHz, DMSO-d6): \( \delta \) 3.75 (3H, s, -OCH3), 3.84 (3H, s, OCH3), 5.66 (1H, s, H-4), 6.77–7.99 (11H, m, Ar-H), 9.36 (1H, s, CONH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): \( \delta \) 45.2, 55.5, 56.3, 56.5, 65.4, 91.1, 91.6, 93.2, 111.5, 112.9, 123.9, 131.9, 139.1, 142.2, 152.0, 159.6, 160.5, 160.6, 161.6, 163.8, 167.2, 186.1, 191.3. MS: m/z = 513.49 [M]+; Analysis: for C28H23N2O7 calcd. C 65.49, H 4.51, N 8.18%; Found C 65.46, H 4.50, N 8.16%.

2.2.10. 5-Benzoyl-2,4-dimethoxyphenyl-3,4-dihydropyrimidine-2(1H)-one-1H-isoindole-1,3(2H)-dione (10). m.p.: 168–170°C; 1H NMR (500 MHz, DMSO-d6): \( \delta \) 3.75 (3H, s, -OCH3), 3.84 (3H, s, OCH3), 5.66 (1H, s, H-4), 6.77–7.99 (11H, m, Ar-H), 9.36 (1H, s, CONH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): \( \delta \) 45.0, 55.5, 56.3, 56.5, 65.4, 91.1, 91.6, 93.2, 111.5, 112.9, 123.9, 131.9, 139.1, 142.2, 152.0, 159.6, 160.5, 160.6, 161.6, 167.2, 186.1, 191.3. MS: m/z = 513.49 [M]+; Analysis: for C29H21N2O6 calcd. C 67.07, H 4.38, N 8.69%; Found C 66.82, H 4.39, N 8.70%.

### Table 1: Physicochemical properties of compounds (1–10).

| Compd. | R                  | % yield |
|--------|--------------------|---------|
| 1      | 3,4-(OCH3)2-C6H3   | 70      |
| 2      | 4-NO2-C6H4         | 75      |
| 3      | 3-NO2-C6H4         | 72      |
| 4      | 2-NO2-C6H4         | 74      |
| 5      | 2,3-(OCH3)2-C6H3   | 68      |
| 6      | 2,4,5-(OCH3)3-C6H3 | 80      |
| 7      | 3,4,5-(OCH3)3-C6H3 | 82      |
| 8      | 2,3,4-(OCH3)3-C6H3 | 80      |
| 9      | 2,4,6-(OCH3)3-C6H3 | 75      |
| 10     | 2,4-(OCH3)2-C6H3   | 70      |

(11H, m, Ar-H), 9.33 (1H, s, CONH, D2O exchg.); 13C NMR (125.76 MHz, DMSO-d6): \( \delta \) 49.5, 56.2, 56.9, 65.4, 99.2, 111.5, 113.1, 123.0, 124.0, 127.5, 129.0, 131.0, 131.9, 134.4, 135.2, 135.4, 138.5, 142.8, 149.7, 151.7, 152.0, 167.2, 191.3. MS: m/z = 513.49 [M]+; Analysis: for C28H23N3O7 calcd. C 65.49, H 4.51, N 8.18%; Found C 65.47, H 4.50, N 8.20%.

### 3. Results and Discussion

As shown in Scheme 1, enaminone, 2-{4-[2(E)-3-(dimethylamino) prop-2-enoyl] phenyl}-1H-isoindole-1,3(2H)-dione (IV), was synthesized by refluxing 2-(4-acetylphenyl)-1H-
isoindole-1,3(2H)-dione (III) with dimethylformamide-dimethylacetal (DMF-DMA) under solvent-free conditions for 12 h. To prepare the final dihydropyrimidinone derivatives, a mixture of substituted benzaldehyde (0.01 mol), enaminone (IV) (0.01 mol), urea (0.01 mol), and glacial acetic acid (10 mL) was heated under reflux for 3 h. The ethylenic protons indicate that the enaminone existed in the $E$-configuration [20]. Compounds presented the D$_2$O exchangeable broad singlet at $\delta$ 9.33–9.62 ppm and $\delta$ 10.12–10.31 ppm corresponding to the two NH protons. The H-4 protons of dihydropyrimidinone moiety and aromatic protons were observed at $\delta$ 5.43–6.17 and $\delta$ 6.59–8.41 ppm, respectively [21]. $^{13}$C NMR spectra confirmed all the carbon atoms for compounds (1–10). Molecular weights of the compounds were confirmed by mass spectral data. Molecular ion peaks were observed in all compounds respective to their molecular weights. The composition of the synthesized compounds (1–10) was confirmed by spectral and elemental data. The possible reaction mechanism involves the acid catalyzed formation of iminium ion intermediate from the substituted aryl aldehydes and urea. Reaction of phthalimide enaminone by iminium ion yields ureidenone, which forms hexahydropyrimidine by cyclization. Final dihydropyrimidinone derivatives (1–10) were obtained by elimination of NH(CH$_3$)$_2$ group from hexahydropyrimidine in presence of glacial acetic acid (Scheme 2).

4. Conclusion
In conclusion, a series of novel dihydropyrimidinone derivatives containing phthalimide moiety were synthesized in good yield, at high level of purity, and in efficient manner from the enaminone, which was derived from phthalimide by simple and solvent-free method. The enaminone existed in the $E$-configuration. All the compounds were characterized and confirmed by different spectroscopic methods and elemental analysis.

Data Availability
Samples of the compounds (1–10) in pure form are available from the authors upon request.

Scheme 2: The possible mechanism for the synthesis of dihydropyrimidinone derivatives containing phthalimide (1–10).
Conflicts of Interest

The authors declare that they have no conflicts of interest.

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