Design, Synthesis, Characterization, and Antimicrobial Activity of Biginelli Products of Indandione

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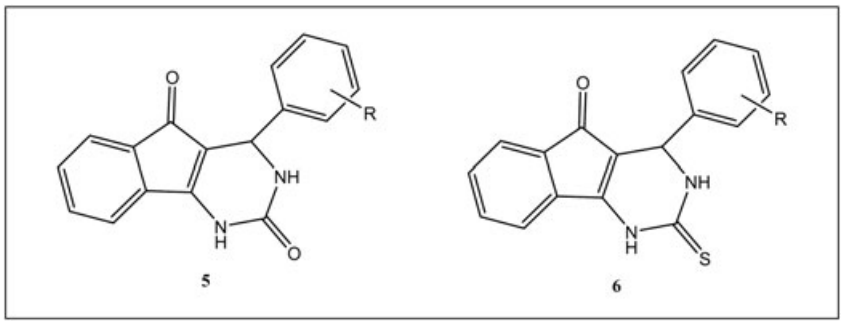

A simple and efficient method has been developed for the synthesis of 4-(substituted phenyl)-3,4-dihydro-1H-indeno [1,2-d] pyrimidine-2,5-dione **(5)** and 4-(substituted phenyl)-2-thioxo-1,2,3,4-tetrahydroindeno [1,2-d] pyrimidine-5-one **(6)**, by a one-pot three component cyclocondensation reaction of 1,3 dicarbonyl compound (Indandione) **(1),** aromatic aldehyde **(2)**, and urea/thiourea **(3/4)** using catalytic amount of conc. HCl in refluxing ethanol. Representative samples were screened for their antimicrobial activity against gram-negative bacteria, *E coli* and *Paeruginosa* and gram-positive bacteria, *S aureus*, and *C diphtheriae* using disc diffusion method. The structures of the products were confirmed by IR, ^{1}H, ^{13}C NMR, and elemental analysis.

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INTRODUCTION

The acid-catalyzed Biginelli reaction, which is a three-component reaction between aldehyde, ß ketoester and urea/thiourea, is a rapid and facile method for the synthesis of pyrimidones, which are interesting compounds with a potential pharmaceutical applications.

The pyrimidone products have been reported to possess biological activities such as antiviral, antibacterial, antihypertensive, and antitumor [1]. More recently pyrimidones have emerged as the integral backbones of several calcium channel blockers [2].

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons [3]. In times where a premium is put on speed, diversity, and efficiency in the drug discovery process [4], MCR strategies offer significant advantages over conventional linear-type synthesis. MCR condensations involve three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials. The search and discovery for new MCR's on one hand [5] and the full exploitation of already known MCRs on the other hand, is therefore of considerable current interest. One such MCR that belongs in the latter category is the venerable Biginelli dihydropyrimidine synthesis. Over the past decade, dihydropyrimidin-2(1H)-ones and their derivatives have attracted considerable attention in organic and medicinal chemistry as the dihydropyrimidine scaffold displays a fascinating array of pharmacological and therapeutic properties. They have emerged as integral backbones of several calcium channel blockers, antihypersentive agents, α-1 antagonists, and neuropeptide Y antagonists [6]. Moreover, several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors. The scope of this pharmacophore has been further increased by the identification of the 4-(3-hydroxyphenyl)-2-thione derivative (±)-4i called monastrol as a novel cell-permeable lead molecule for the development of new anticancer drugs [7].

Keeping in view the high synthetic utility and pharmacological importance, we report here the synthesis of substituted Pyrimidones 3,4-dihydropyrimidin-2(1H)-one (DHPMs).

RESULTS AND DISCUSSION

In 1983, the Italian Chemist Pietro Biginelli reported on the acid- catalyzed cyclocondensation reaction of ethylacetoacetate, benzaldehyde and Urea [8]. The reaction was performed simply by heating a mixture of the three components dissolved in ethanol with catalytic amount of HCl at refluxed temperature. Product of these novel one pot, three component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as DHPM.

Thus, the target molecules 4-(substituted phenyl)-3,4-dihydro-1H-indeno [1,2-d] pyrimidine-2,5-dione **(5a-e)** and 4-(substituted phenyl)-2-thioxo-1,2,3,4-tetrahydroindeno [1,2-d] pyrimidine-5-one **(6a-e)** were synthesized in good yield by the one pot reaction of aromatic aldehydes, Indandione [9] and urea/thiourea in refluxing ethanol using few drops of conc. HCl as catalyst. The pathway of synthesis of compounds **5** and **6** is given in Scheme 1.

The spectral Analysis of Some representative compounds is given below:

4-Phenyl-3,4-dihydro-1H-indeno [1,2-d] pyrimidine-2,5-dione (5a). Yield: 84 %; m.p.=175–178°C: IR (cm^{-1}): 1658(C═O), 1715(C═O), 3268(NH), ^{1}H NMR(DMSO-d_6,δ/ ppm): 6.74 (s, 1H, CH), 7.24–8.03 (m, 9H, Ar—H), 8.73 (s, 2H, 2xNH), ^{13}C NMR(DMSO-d_6,δ/ ppm): 114.29 (CH), 119.46–132.9 (C═C,Ar—C),180.28 (C═O),186.2 (C═O): Anal. Calcd for $C_{17}H_{12}N_20_2$: C, 73.91; H, 4.35; N, 10.14%.Found: C, 73.87; H, 4.32, N, 10.24%.

4-(4-Chlorophenyl)-3, 4-dihydro-1H-indeno [1,2-d] pyrimidine-2,5-dione (5b). Yield: 86%; m.p. = 215–217°C: IR (cm^{-1}): 1667(C═O), 1742(C═O), 3275(NH), ^{1}H NMR(DMSO-d_6,δ/ ppm): 6.48 (s,1H, CH), 6.89–7.64 (m,8H, Ar—H), 8.91 (s,2H, 2xNH), ^{13}C NMR(DMSO-d_6,δ/ ppm): 113.89 (CH), 117.98-134.84 (C═C, Ar—C), 180.43 (C═O), 188.45 (C═O): Anal. Calcd for $C_{17}H_{11}N_20_2Cl$: C, 65.70; H, 3.54; N, 9.01%. Found: C, 65.62; H, 3.42, N, 9.12%.

4-(4-Methoxyphenyl phenyl)-3,4-dihydro-1H-indeno [1,2-d] pyrimidine-2,5-dione (5c). Yield: 88%; m.p. = 180–183°C: IR (cm^{-1}): 1660(C═O), 1730(C═O), 3290 (NH), ^{1}H NMR (DMSO-d_6,δ/ ppm): 3.88 (s, 3H, OCH_3), 6.63 (s, 1H, CH),7.11–7.93 (m, 8H, Ar—H), 8.6 (s, 2H, 2xNH), ^{13}C NMR(DMSO-d_6,δ/ppm): 55.70 (OCH_3), 115.10 (CH), 116.36-131.7 (C═C, Ar—C),179.56 (C═O), 187.9 (C═O): Anal. Calcd for $C_{18}H_{14}N_20_3$: C, 70.59; H, 4.58; N, 9.15%. Found: C, 70.62; H, 4.52, N, 9.24%.

4-(2-Hydroxy phenyl)-3,4-dihydro-1H-indeno [1,2-d] pyrimidine-2,5-dione (5d). Yield:83%; m.p. = 200–202° C: IR (cm^{-1}): 1657 (C═O), 1765 (C═O), 3310 (NH), ^{1}H NMR (DMSO-d_6,δ/ppm): 4.12 (s,1H, OH),6.82 (s, 1H, CH), 7.42–8.13 (m, 8H, Ar—H), 8.86 (s, 2H, 2xNH), ^{13}C NMR(DMSO-d_6,δ/ppm): 114.25 (CH), 117.46–130.8 (C═C, Ar—C), 178.82 (C═O), 184.47 (C═O): Anal. Calcd for $C_{17}H_{12}N_20_3$: C, 69.86; H, 4.11; N, 9.59%. Found: C, 69.82; H, 4.21, N, 9.54%.

4-(4-Hydroxy-3-methoxyphenyl)-3,4-dihydro-1H-indeno [1,2-d] pyrimidine-2,5-dione (5e). Yield: 87%; m.p. = 220–223°C: IR (cm^{-1}): 1660 (C═O), 1750 (C═O), 3290 (NH), ^{1}H NMR (DMSO-d_6,δ/ppm): 3.56 (s, 3H, OCH_3), 5.24 (s, 1H, OH), 6.63 (s, 1H, CH),7.4–7.9 (m, 7H, Ar—H), 8.8 (s, 2H, 2xNH). Anal. Calcd for $C_{18}H_{14}N_20_4$: C, 67.08; H, 4.35; N, 8.72%. Found: C, 67.12; H, 4.42, N, 8.64%.

4-(Phenyl)-2-thioxo-1,2,3,4-tetrahydroindeno [1,2-d] pyrimidine-5-one (6a). Yield: 82%; m.p. = 249–252°C: IR (cm^{-1}): 1680 (C═O), 1240 (C═S), 3310 (NH), ^{1}H NMR (DMSO-d_6,δ/ ppm): 6.85 (s,1H, CH),7.05–7.46 (m, 9H, Ar—H), 9.26 (s, 2H, 2xNH): Anal. Calcd for $C_{17}H_{12}N_20S$: C, 69.86; H, 4.11; N, 9.59%. Found C, 69.82; H, 4.18, N, 9.54%.

4-(4-Chlorophenyl)-2-thioxo-1,2,3,4-tetrahydroindeno [1,2-d] pyrimidine-5-one (6b). Yield: 88%; m.p. = 185–187°C: IR (cm^{-1}): 1662 (C═O), 1218 (C═S), 3328 (NH): ^{1}H NMR (DMSO-d_6,δ/ppm): 6.54 (s,1H, H), 7.86–8.65 (m, 8H, Ar—H), 10.2(s, 2H, 2xNH): ^{13}C NMR (DMSO-d_6,δ/ ppm): 116.12 (CH), 119.96–138.67 (C═C, Ar—C),184.8 (C═O), 189.65 (C═S): Anal. Calcd for $C_{17}H_{11}N_20SCl$: C, 62.48; H, 3.37; N, 8.58%. Found: C, 62.35; H, 3.32, N, 8.64%.

4-(4-Methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydroindeno [1,2-d] pyrimidine-5-one (6c). Yield: 87%; m.p. = 144–147°C : IR (cm^{-1}): 1670 (C═O), 1230(C═S), 3330(NH): ^{1}H NMR (DMSO-d_6,δ/ppm): 3.88 (s,3H, OCH_3), 6.72 (s,1H, H), 7.75–8.70 (m,8H, Ar—H), 10.6 (s, 2H, 2xNH): ^{13}C NMR(DMSO-d_6,δ/ppm): 55.65 (OCH_3), 114.29 (CH), 120.56–139.8 (C═C, Ar—C), 182.7 (C═O), 184.34 (C═S): Anal. Calcd for $C_{18}H_{14}N_20_2S$: C, 67.08; H, 4.35; N, 8.70%. Found: C, 67.15; H, 4.22, N, 8.74%.

Scheme 1. Pathway of synthesis of compounds **5** and **6**.

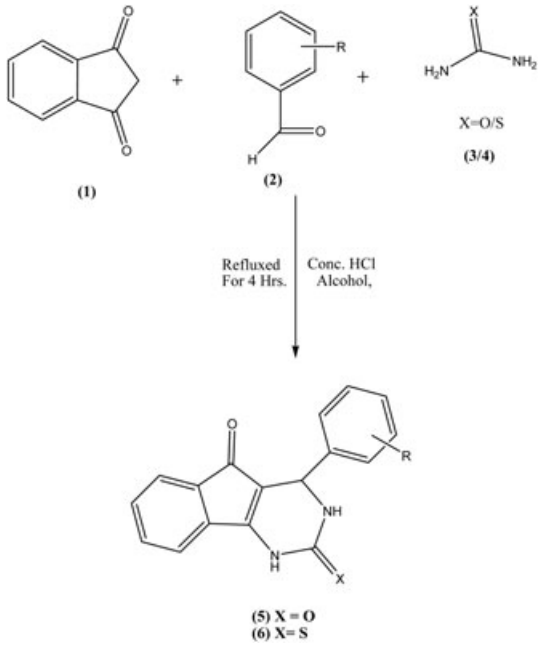

Table 1

Physical data of compounds **5** and **6**.

Compounds	R	Molecular formula	M.p. (°C)	Yield (%)
5a	H	$C_{17}H_{12}N_20_2$	175–178	84
5b	4—Cl	$C_{17}H_{11}N_20_2Cl$	215–217	86
5c	4—OCH_3	$C_{18}H_{14}N_20_3$	180–183	88
5d	2 OH	$C_{17}H_{12}N_20_3$	200–202	83
5e	4—OCH_3, 2—OH	$C_{18}H_{14}N_20_4$	220–223	87
6a	H	$C_{17}H_{12}N_20S$	249–252	82
6b	4—Cl	$C_{17}H_{11}N_20SCl$	185–187	88
6c	4—OCH_3	$C_{18}H_{14}N_20_2S$	144–147	87
6d	2—OH	$C_{17}H_{12}N_20_2S$	240–243	84
6e	4—OCH_3, 2—OH	$C_{18}H_{14}N_20_3S$	196–198	89

4-(2-Hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydroindeno [1,2-d] pyrimidine-5-one (6d). Yield: 84%; m.p. = 240–243°C: IR (cm^{-1}): 1680 (C═O), 1245 (C═S), 3290 (NH): ^{1}H NMR (DMSO-d_6,δ/ppm): 4.82 (s,1H, OH), 6.87 (s,1H, H), 7.58–8.46 (m,8H, Ar—H), 10.42 (s, 2H, 2xNH): ^{13}C NMR (DMSO-d_6,δ/ ppm): 115.48 (CH), 121.86–136.54 (C═C, Ar—C), 181.6(C═O), 188.28 (C═S): Anal. Calcd for $C_{17}H_{12}N_20_2S$: C, 66.23; H, 3.89; N, 9.09%. Found: C, 66.25; H, 3.97, N, 8.98%.

4-(4-Hydroxy-3-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydroindeno [1,2-d] pyrimidine-5-one (6e). Yield: 89%; m.p. = 196–198°C: IR (cm^{-1}): 1680 (C═O), 1280 (C═S), 3360 (NH),^{1}H NMR (DMSO-d_6,δ/ ppm): 3.92 (s, 3H, OCH_3), 5.24 (s, 1H, OH) 6.72 (1H, s, CH), 7.75–8.70 (m, 7H, Ar—H), 10.6 (2H, s, 2xNH), Anal. Calcd for $C_{18}H_{14}N_20_3S$: C, 63.91; H, 4.14; N, 8.28%. Found: C, 63.98; H, 4.18, N, 8.35%.

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis of 3, 4-dihydropyrimidin-2(1H)-one. Indandione **1**(0.05 mol), (0.05 mol) Aromatic aldehydes **2** and urea/thiourea **3/4** (0.05 mol) was refluxed on a water bath in ethanol in the presence of catalytic amount of conc. HCl. The progress of the reaction was monitored by TLC. After completion of the reaction, the concentrated reaction mixture was cooled and poured onto ice-cold water, solid separated was filtered off, dried, and recrystallized from absolute alcohol to obtain pure compound (**5/6**).

The physical data is given in Table 1.

Antimicrobial and antifungal activities. All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method [10,11]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The data is given in Table 2.

Table 2

Antibacterial activity of compound **5** and **6**.

	Zone of inhibition (in mm)			
	Gram positive		Gram negative	
Comp.	*S. aureus*	*C. diphtheria*	*P. aeruginosa*	*E. coli*
5b	22	20	21	19
5c	21	18	20	18
5d	18	19	18	14
5e	16	18	17	18
6b	21	22	16	17
6c	20	21	18	15
6d	18	19	21	14
6e	17	21	21	16
Amphicilin trihydrate	26	28	24	21
DMSO	0	0	0	0

Concentration of the compounds taken was about 100 μg/mL.
[a] Diameter of the disc was 6 mm.

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