(E)-3-(2,5-Dimethoxyphenyl)-1-{[4-(2,5-dimethoxyphenyl)-6-((E)-2,5-dimethoxystyryl)-2-thioxo-1,2,3,4tetrahydropyrimidin-5-yl]}prop-2-en-1-one and (E)-3(2,5-Dimethoxyphenyl)-1-{[4-(2,5-dimethoxyphenyl)

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(*E*)-3-(2,5-Dimethoxyphenyl)-1-{[4-(2,5-dimethoxyphenyl)-6-((*E*)-2,5-dimethoxystyryl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]}prop-2-en-1-one and (*E*)-3-(2,5-Dimethoxyphenyl)-1-{[4-(2,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]}prop-2-en-1-one

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Abstract: Dihydropyrimidine derivatives possess great potential to be used as a precursor for the synthesis of wide diverse dihydropyrimidine-like derivatives. In this research, the title compounds were synthesized through the reaction between 5-acetyl-4-(2,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione and 2,5-dimethoxybenzladehyde under aldol condensation condition. The title compound, (*E*)-3-(2,5-dimethoxyphenyl)-1-{[(4-(2,5-dimethoxyphenyl)-6-((*E*)-2,5-dimethoxystyryl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)]}prop-2-en-1-one (yield 15%), was obtained as major product, whereas (*E*)-3-(2,5-dimethoxyphenyl)-1-{[(4-(2,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidin-5-yl)]}prop-2-en-1-one (yield 8%) as side product through vinylogous aldol condensation.

Keywords: 5-acetyl-4-(2,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione; aldol condensation; vinylogous aldol condensation

1. Introduction

The derivatives of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) as products of the Biginelli reaction are known to have various pharmacological activities, such as anticancer [1], antioxidant [2], anti-inflammation, antibacterial, and antifungal [3], anti HIV [4], and antihypertensive [5]. The discovery of 4-(3-hydroxyphenyl)-3,4-dihydropyrimidine-2(1*H*)-thione, which is well known as monastrol (**1**) as moderate anticancer agent through inhibition of the microtubule-stimulated ATPase activity of Eg5 [6] inspired researchers to use this protein as a protein target to develop new anticancer agents due to its specific function during cell cycle. Replacement of ester group at the 5-position of monastrol with acyl group enhances its potency when compared with the racemic monastrol [7], whereas replacement with cyclohexanone ring (enastron (compound **2**) and dimethylenastron (compound **3**), Figure 1) significantly increased their inhibitor activity as compared to monastrol [8].

Based on the information, we focus our study on finding anticancer compounds from the 5-acyl-3,4-dihydropyrimidine-2-thione family.

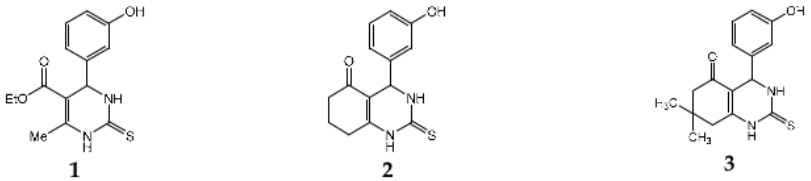

Figure 1. Replacement of ester group of monastrol (**1**) with acyl group increases anticancer activity.

From the organic synthesis point of view, acetyl group at five-position is a potential moiety for introducing the benzylidene group to form a chalcone analogue using aldol condensation, whereas the methyl group of six-position can be transformed into styryl moiety through vinylogous aldol condensation. Compounds with such structure are known for their antimicrobial and cytotoxicity activity, and have already been prepared by the Biginelli reaction using (thio)urea, derivatives of benzaldehyde, and curcumin as 1,3-dicarbonyl component [6]. However, this reaction route required an additional reaction step of curcumin or its derivatives to be prepared. Herein, we reported the synthesis of the 5,6-dibenzylidene DHPM-type (**6**) and 5-benzylidene DHPM-type (**5**) employing aldol condensation while using a 5-acetyl-6-methyl DHPM derivative as precursor.

2. Results and Discussion

The synthesis of the title compounds were performed in two steps, firstly the synthesis of a DHPM derivative (compound **4**) from acetylacetone, 2,5-dimethoxybenzaldehyde, and thiourea using Biginelli reaction. Compound **4** was then used as a precursor to synthesize the title compounds **5** and **6** by reaction with 2,5-dimethoxybenzaldehyde under aldol condition, as presented in Figure 2.

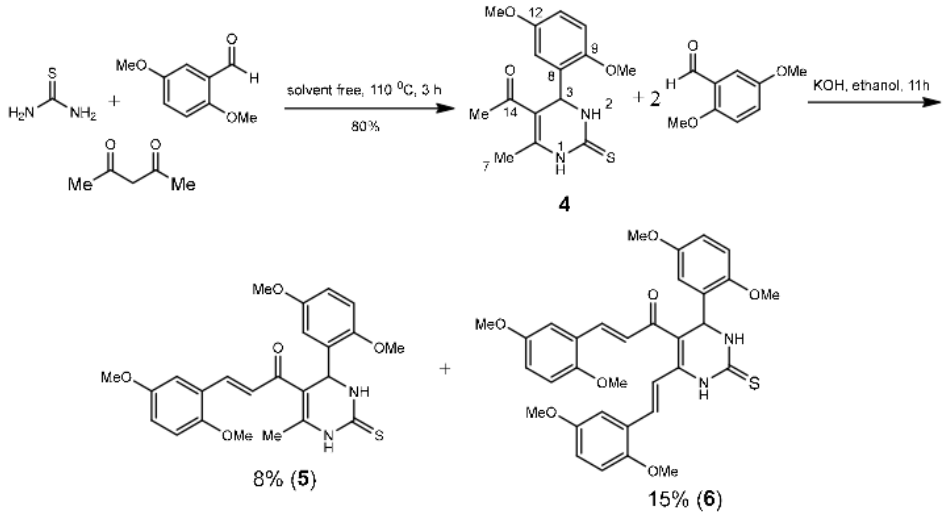

Figure 2. Synthesis reaction of the title compounds.

The synthesis of compound **4** was performed following the previous article [7] with slight modification (differed in purification steps). Compound **4** was then used as precursor to synthesize title compounds **5** and **6** by reaction with 2,5-dimethoxybenzaldehyde under the aldol condition. The reaction progress was monitored by thin layer chromatography (TLC) until completion. During TLC

experiment, compound **5** was firstly observed, whereas compound **6** appeared later. At the end of the reaction, only these two spots were observed. This observation supported that the first step reaction is the introduction of the benzylidene moiety on the acetyl group [9]. The crude reaction product was then separated on column chromatography using silica gel as the stationary phase and chloroform: ethyl acetate (10:1) as mobile phase. After separation with column chromatography, we obtained 8% yield for compound **5** and 15% for compound **6**.

5-Acetyl-4-(2,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (**4**): colorless needle crystal (481 mg, 80%), R_f 0.48 (*n*-hexane: ethyl acetate = 2:1); m.p 266–268 °C (EtOH-H_2O), HRMS (ESI) $[M + Na]^+$ calcd. for $[C_{15}H_{18}N_2O_3SNa]^+$ = 329.0936 found = 329.0952, IR (cm^{-1}): 3215 (N-H), 2981 (C-H aromatic), 2833 (aliphatic C-H), 1633 (conjugated C=O), 1573, 1496, 1469 (aromatic C=C-), 1249 (C_{aryl}-O-C_{alkyl}), 1176 (-C=S); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H (ppm) 7.93 (s, 1H), 7.46 (s, 1H), 5.75 (d, *J* = 3.3 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 6,79 (dd, *J* = 9.0, 2.9 Hz, 1H), 6.59 (d, *J* = 3.0 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 2.40 (s, 3H), 2.04 (s, 3H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ_H (ppm) 195.8, 174.7, 154.0, 150.6, 143.9, 129.0, 114.4, 113.2, 111.5, 108.0, 56.0, 55.8, 50.9, 29.5, 19.3.

The mass determination of compound **4** exhibited $[M + Na]^+$ ion at *m*/*z* 329.0952, which closed to the theoretical value of 329.0936 and was suitable for the molecular formula of $C_{15}H_{18}N_2O_3SNa$ (Supplementary Material, Figure S1). The analysis of IR spectra showed the existence of N-H amide, C-H aromatic, C-H aliphatic, conjugated C=O, C=C aromatic, C_{alkyl}-O-C_{aryl} ether, and C=S bonds, which were consecutively indicated by bands at $\tilde{\nu}$ (cm^{-1}) 3215, 2981, 2833, 1633, 1573–1469, 1249, and 1176 [10] (Figure S2). The nuclear magnetic resonance (NMR) data of compound **4** are presented in Table 1. The existence of the dihydropyrimidine ring was assigned by following signals: proton signal of chiral C-4 at δ_H 5.75 ppm (d, $^3J_{HH}$ = 3.3 Hz, 1H), proton of N-3 at δ_H 7.46 ppm (s, 1H), proton of N-1 at δ_H 7.93 ppm (s, 1H), and ^{13}C signal of C-5 and C-6 at δ_C at 108.0 ppm and 143.9 ppm. The acetyl group was assigned by methyl signal at δ_H 2.40 ppm (s, 3H) and carbonyl signal at δ_C 195.8 ppm, while the methyl group at C-7 appeared as single signal at δ_H 2.04 ppm. Three aromatic proton signals with ABX system were assigned, as follows: one aromatic proton with *ortho* and *meta* coupling (δ_H 6.79 ppm (dd, *J* = 9.0 and 2.9 Hz, 1H)), one aromatic proton with *ortho* coupling (δ_H 6.84 ppm (d, *J* = 8.8 Hz, 1H)), and one aromatic proton with *meta* coupling (δ_H 6.59 ppm (d, *J* = 3.0 Hz, 1H)). Two methoxy groups appeared at δ_H 3.86 ppm (s, 3H) and δ_H 3.72 ppm (s, 3H) (Figure S3 for ^{1}H-NMR and Figure S4 for ^{13}C-NMR).

Table 1. Nuclear magnetic resonance (NMR) data of compound **4** in $CDCl_3$.

No. Atom	δ_H (Mult, *J* Hz)	δ_C (ppm)
1	7.93 (s, 1H)	-
2	-	174.7
3	7.46 (s, 1H)	-
4	5.75 (d, *J* = 3.3 Hz, 1H)	50.9
5	-	108.0
6	-	143.9
7	2.04 (s, 3H)	19.3
8	-	129.0
9	-	154.0
9-OMe	3.86 (s, 3H)	56.3
10	6.84 (d, *J* = 9.0 Hz, 1H)	114.4
11	6.79 (dd, *J* = 9.0, 3.0 Hz, 1H)	113.2
12	-	150.6
12-OMe	3.72 (s, 3H)	55.8
13	6.59 (d, *J* = 3.0 Hz, 1H)	111,5
14	-	195.8
15	2.40 (s, 3H)	29.5

(E)-3-(2,5-Dimethoxyphenyl)-1-{[4-(2,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]}prop-2-en-1-one (**5**). Yellow needle crystal (38 mg, 8%); m.p 154–156 °C (EtOH-H_2O); UV-Vis (EtOH) λ_{max} (nm) 298 (log ε = 3.98); 372 (log ε = 3.98) (Figure S5); HRMS (ESI): calcd. for $[C_{24}H_{26}N_2NaO_5S]^+$ = 477.1460 found = 477.1457; IR (cm^{-1}): 3174 (N-H), 3005 (aromatic C-H), 2978 (aliphatic C-H), 1680 (conjugated C=O), 1645 (conjugated C=C), 1580, 1493, 1427 (aromatic C=C), 1279 (C_{alkyl}-O-C_{aryl}), 1173 (C=S). ^{1}H-NMR (400 MHz, Acetone-d_6) δ_H (ppm): 9.19 (s, 1H), 8.30 (s, 1H), 7.77 (d, *J* = 15.8 Hz, 1H), 7.18 (d, *J* = 15.7 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 6.97–6.94 (m, 2H), 6.84 (d, *J* = 3.1 Hz, 1H), 6.83–6.79 (m, 2H), 5.92 (d, *J* = 3.4 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 2.46 (s, 3H). ^{13}C-NMR (101 MHz, Acetone-d_6) δ_C (ppm): 189.05, 176.64, 154.80, 154.62, 153.89, 151.48, 143.63, 137.41, 132.08, 126.76, 125.26, 117.76, 115.29, 113.97, 113.66, 113.54, 112.86, 110.86, 56.44, 56.39, 56.04, 55.79, 51.28, 18.41.

(E)-3-(2,5-Dimethoxyphenyl)-1-{[4-(2,5-dimethoxy-phenyl)-6-((E)-2,5-dimethoxystyryl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]}prop-2-en-1-one (**6**): Yellow needle crystal (90 mg, 15%); m.p 212–214 °C (EtOH-H_2O); UV-Vis (EtOH) λ_{max} (nm) 291 (log ε = 4.44), 389 (log ε = 4.21) (Figure S12); HRMS (ESI): calcd. for $[C_{33}H_{34}N_2NaO_7S]^+$ = 625.1984 found = 625.1981 ; IR (cm^{-1}): 3198 (N-H), 2945 (aliphatic C-H), 1624 (conjugated C=O), 1578, 1562, 1495 (aromatic C=C), 1276 (C_{alkyl}-O-C_{aryl}), 1225 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.36 (d, *J* = 1.1 Hz, 1H), 9.41 (dd, *J* = 3.8, 1.4 Hz, 1H), 7.59 (d, *J* = 15.8 Hz, 1H), 7.43 (d, *J* = 16.4 Hz, 1H), 7.37 (d, *J* = 16.4 Hz, 1H), 7.25 (d, *J* = 15.8 Hz, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 7.10 (d, *J* = 2.7 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.95–6.93 (m, 3H), 6.89 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.85 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.70 (d, *J* = 3.0 Hz, 1H), 5.59 (d, *J* = 4.0 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.60 (s, 3H). ^{13}C-NMR (101 MHz, DMSO-d_6) δ_C (ppm): 188.66, 175.10, 153.21, 153.10, 153.04, 152.41, 151.73, 150.33, 141.15, 135.04, 131.76, 130.79, 127.05, 124.94, 123.61, 120.65, 117.48, 116.07, 114.06, 112.93, 112.88, 112.56, 112.32, 112.31, 112.26, 112.18, 55.91, 55.90, 55.85, 55.33, 55.32, 55.29, 49.91.

Numbering of the molecular structure and selected HMBC correlation of compound **5** are presented in Figure 3, and in Figure 4 for compound **6**. Mass determination of compounds **5** and **6** showed $[M + Na]^+$ ion at *m*/*z* 477.1457 for compound **5** (Figure S6) and *m*/*z* 625.1981 for compound **6** (Figure S13), respectively, which were closed to the theoretical value of 477.1460 and 625.1984. Infrared spectra of both compounds **5** and **6** showed vibration bands of N-H amide, C-H aliphatic, conjugated C=O, C=C aromatic, C_{alkyl}-O-C_{aryl}, and C=S bonds consecutively at wave numbers (cm^{-1}): 3174, 2978, 1680 1580, 1279, and 1173 for compound **5** (Figure S7), and 3198, 2945, 1624, 1578, 1276, and 1225 for compound **6** (Figure S14). The existence of two alkene groups with the *trans* configuration of compound **6** were assigned by four doublet proton signals at chemical shift of δ_H 7.59 and 7.25 ppm (*J* = 15.8 Hz) and signals at δ_H 7.43 and 7.37 ppm (*J* = 16.4 Hz) (Figure S15), whereas the existence of an alkene group in compound **5** was assigned by two doublet proton signals at δ_H 7.77 and 7.18 ppm (*J* = 15.8 Hz) (Figure S8).

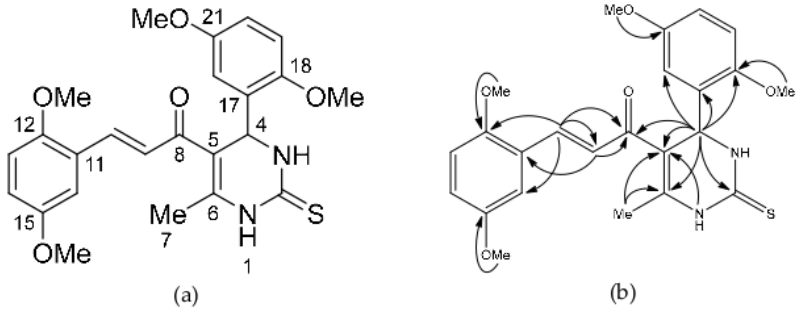

Figure 3. (**a**) Numbering of the structure, and (**b**) selected HMBC correlation for compound **5**.

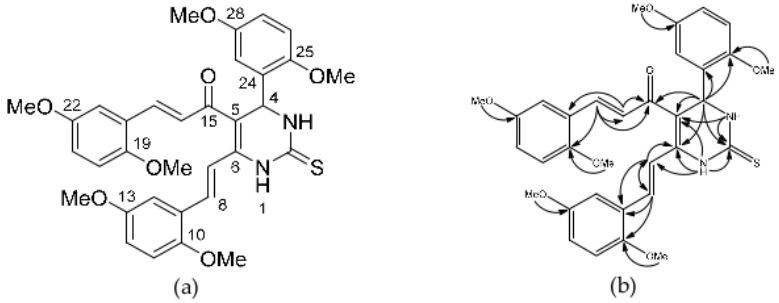

Figure 4. (**a**) Numbering of the structure, and (**b**) selected HMBC correlation for compound **6.**

Two-dimensional NMR experiments (Heteronuclear Multiple Quantum Coherence (HMQC) and Heteronuclear Multiple Bond Correlation (HMBC)) were performed to prove that aldol condensation proceeded at C-8. The methyl olefinic fragment at δ_H 2.46 ppm proceeded a long range correlation with carbon signal at C 110.86 ppm (C-5) and 143.63 ppm (C-6) (Compound **5**). The HMBC correlation tables of compounds **5** and **6** are presented in Table 2, Table 3, respectively. The ^{13}C-NMR spectra of compound **5** exhibited 24 signals that represented all carbon atoms of compound **5** (Figure S9), while the ^{13}C-NMR spectra of compound **6** showed 33 signals reflected all the carbon atoms of compound **6** (Figure S16). The structures of compounds **5** and **6** are consistent with the molecular mass.

Table 2. NMR data of compound **5** in Acetone-d_6.

No. Atom	δ_H (ppm), mult, *J* (Hz)	δ_C (ppm)	HMBC
1	9.19 (s, 1H)		C-5
2		176.64	
3	8.30 (s, 1H)		
4	5.92 (d, *J* = 3.4 Hz, 1H)	51.28	C-2, C-5, C-6, C-8 C-17, C-18, C-22
5		110.86	
6		143.63	
7	2.46 (s, 3H)	18.41	C-5, C-6
8		189.05	
9	7.18 (d, *J* = 15.8 Hz, 1H)	126.76	C-11
10	7.77 (d, *J* = 15.8 Hz, 1H)	137.41	C-8, C-9, C-12, C-16
11		125.26	
12		153.89	
12-OCH_3	3.81 (s, 3H)	56.39	C-12
13	6.83–6.79 (m, 2H)	113.54	
14	6.83–6.79 (m, 2H)	117.76	
15		154.62	
15-OCH_3	3.77 (s, 3H)	56.04	C-15
16	7.13 (d, *J* = 2.6 Hz, 1H)	113.97	C-10, C-12, C-14
17		132.08	
18		151.48	
18-OCH_3	3.84 (s, 3H)	56.44	C-18
19	6.97–6.94 (m, 2H)	112.86	
20	6.97–6.94 (m, 2H)	113.66	
21		154.80	
21-OCH_3	3.69 (s, 3H)	55.79	C-21
22	6.84 (d, *J* = 3.1 Hz, 1H)	115.29	C-18, C-20, C-21

Table 3. NMR data of compound **6** in DMSO-d_6.

No. Atom	δ_H (ppm), mult, *J* (Hz)	δ_C (ppm)	HMBC
1	10.36 (d, *J* = 1.4 Hz, 1H)		C-2, C-5, C-6, C-7
2		175.10	
3	9.41 (dd, *J* = 4.0, 1.4 Hz, 1H)		C-2, C-5
4	5.59 (d, *J* = 4.0 Hz, 1H)	49.91	C-2, C-5, C-6, C-15, C-24, C-25
5		112.18	
6		141.15	
7	7.37 (d, *J* = 16.4 Hz, 1H)	120.65	C-6, C-8, C-9
8	7.43 (d, *J* = 16.4 Hz, 1H)	131.76	C-6, C-7, C-10
9		124.94	
10		151.73	
10-OCH_3	3.69 (s, 3H)	55.33	C-10
11	6.95–6.93 (m, 3H)	112.88	
12	6.89 (dd, *J* = 9.0, 3.0 Hz, 1H)	116.07	C-10
13		153.10	
13-OCH_3	3.64 (s, 3H)	55.90	C-13
14	7.11 (d, *J* = 3.0 Hz, 1H)	112.31	C-8, C-10, C-12
15		188.66	
16	7.25 (d, *J* = 15.8 Hz, 1H)	127.05	C-15, C-18
17	7.59 (d, *J* = 15.8 Hz, 1H)	135.04	C-15, C-16, C-19
18		123.61	
19		152.41	
19-OCH_3	3.68 (s, 3H)	55.85	C-19
20	6.95–6.93 (m, 3H)	112.93	
21	6.95–6.93 (m, 3H)	117.48	
22		153.21	
22-OCH_3	3.60 (s, 3H)	55.91	C-22
23	7.10 (d, *J* = 2.7 Hz, 1H)	112.26	C-17, C-21, C-25
24		130.79	
25		150.33	
25-OCH_3	3.73 (s, 3H)	55.29	C-25
26	6.97 (d, *J* = 8.8 Hz, 1H)	112.56	
27	6.85 (dd, *J* = 8.9, 3.1 Hz, 1H)	112.32	C-25, C-29
28		153.04	
28-OCH_3	3.66 (s, 3H)	55.32	C-28
29	6.70 (d, *J* = 3.0 Hz, 1H)	114.06	C-25, C-27

3. Materials and Methods

3.1. General

The chemicals were provided from the commercial sources with pro analysis or pro synthesis grade and were used without prior purification. Thin layer chromatography was conducted on silica gel GF_{254} plate (E Merck, Darmstadt, Germany) for the monitoring of the reaction progress and test of purity. The spots of TLC were identified by UV lamp (λ 254 nm). The UV spectrum was recorded on a UV-Vis spectrophotometer type UV-1800 (Shimadzu, Kyoto, Japan). The mass spectra were measured on a HRESIMS QTOF micrOTOF-Q II Bruker Daltonics (Billerica, MA, USA). The Fourier transform infrared (FTIR) spectrum was recorded on an IRTracer100 spectrophotometer (Shimadzu, Kyoto, Japan) while using the diffuse reflectance method. The nuclear magnetic resonance (NMR) spectrum (^{1}H-, and ^{13}C-APT) was recorded on a JEOL JNM-ECS400 spectrometer (at 400 and 100 MHz) (JEOL Ltd., Tokyo, Japan), with Acetone-d_6, $CDCl_3$ and DMSO-d_6 as the solvent and internal standard.

3.2. Synthesis of Compound **4**

In a screw-capped vial, the mixture of 2,5-dimethoxybenzaldehyde (0.331 g, 2 mmol), acetyl acetone (0.2 g, 2 mmol), and thiourea (0.19 g, 2.5 mmol) was heated without stirring at 110 °C for 3 h [7]. The reaction mixture was then allowed to cool to room temperature, dissolved in ethanol, then added with water dropwise, and the precipitate was filtered off. The solid was then recrystallized using aqueous ethanol.

3.3. Synthesis of the Title Compounds

Compound **4** (0.306 g, 1 mmol), 2,5-dimethoxybenzaldehyde (0.414 g, 2.5 mmol), KOH (0.056 g, 1 mmol), and ethanol (10 mL) were placed in a three neck round bottom flask that was equipped with a reflux condenser. The reaction mixture was refluxed at 50 °C for 11 h and then cooled to room temperature. The reaction mixture was poured to ice-water, neutralized with HCl-ethanolic solution, and the precipitate was filtered off. The crude product was then subjected to a silica gel column chromatography while using *n*-hexane:ethyl acetate (10:1) as eluent to furnish the title compounds (compounds **5** and **6**).

4. Conclusions

In conclusion, we have synthesized two new compounds (*E*)-3-(2,5-Dimethoxyphenyl)-1-{[4-(2,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]}prop-2-en-1-one (compound **5**) and (*E*)-3-(2,5-Dimethoxyphenyl)-1-{[4-(2,5-dimethoxy-phenyl)-6-((*E*)-2,5-dimethoxystyryl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl]}prop-2-en-1-one (compound **6**) under aldol condensation condition.

Supplementary Materials: FTIR, HRMS (ESI), ^{1}H-NMR and ^{13}C-APT-NMR, HMBC and HMQC spectra of the prepared compounds are available on line.

Author Contributions: H.S. brought the idea, managed the research, and prepared the manuscript. N.K., E.S., and Y.A. conducted the experiment, K.U.H. brought the idea and did the structure elucidation, I.I. did structure elucidation, A.N.K. corrected the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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