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Synthesis of New Pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione Derivatives

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Abstract—The condensation of 5-acetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione with 3-fluoro-, 4-fluoro-, and 2-methoxy-3,5-dichlorobenzaldehydes and methyl (4-formyl-2- oxo-2*H*-chromen-7-yl)carbamate in BuOH in the presence of piperidine and acetic acid for 4 h under reflux gave 5-[(*E*)-3-aryl-2-propenoyl]pyrimidine--2,4,6(1*H*,3*H*,5*H*)-triones) and methyl *N*-{2-oxo-4-[(*E*)-3-oxo-3-(2,4,6-trioxohexahydropyrimidin-5-yl)-1-propenyl]-2*H*-chromen-7-yl}carbamate. The reactions of 3-methoxy-4-hydroxy-, 3,5-dimethoxy-4-hydroxybenzaldehydes with 5-acetyl-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione in dioxane in the presence of boron trifluoride etherate at room temperature forms the corresponding chalcones within 48 h. The corresponding imines and 5-arylidene derivatives were prepared by the condensation of barbituric acid with alkyl *C*-nitroso phenylcarbamates in methanol and hydroxy-substituted benzaldehydes in water. The condensation of 5-[(4-hydroxy-3,5-dimethoxyphenyl)methylene]-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones with aminoguanidine bicarbonate results in the formation of 7-hydrazinyl-5-(4-hydroxy-3,5-dimethoxyphenyl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione. The cyclocondensation of pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione with methyl *N*-{3-[(*E*)-3-(4-methoxyphenyl)-2-propenoyl]phenyl}carbamate in acetic acid in the presence of P_2O_5 provided methyl {3-[5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-7-yl]phenyl}carbamate.

Keywords: pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, 5-arylidene barbituric acid, 5-acetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, chalcones pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione hybrids, cyclocondensation, aromatic and heterocyclic aldehydes, alkyl *N*-(4-nitroso(amino)phenyl)carbamates

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INTRODUCTION

Pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione and its derivatives are currently being intensively studied, which is primarily explained by their high antimicrobial activity. Among them, compounds with anti-inflammatory, antitumor, antiviral, analgesic, and sedative activity have also been found [1]. Deotale and Dhonde [2] have recently described the synthesis of a new class of pyrimidinetrione hydrazones. In addition, the structure–activity relationships with respect to fungal growth inhibition for two clinically significant fungal pathogens have been studied. A number of derivatives, including 5-acylpyrimidinetrione arylhydrazones have been found to strongly inhibit the growth of pathogens at a concentration of 10 μL or lower with a minimal level of toxicity in mammals.

In view of the aforesaid, the development of synthetic approaches to new functionally substituted derivatives of barbituric acid with potential biological activity is a relevant task of modern organic and medicinal chemistry. The knowledge that the modification of barbituric acid in position *5* imparts an enhanced therapeutic activity to the resulting 5-substituted system prompts researchers to synthesize new such derivatives and study their antibacterial activity.

Of great interest in the synthesis of new functionally substituted pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione derivatives is the readily available 5-acyl derivative, which is prepared by the acylation of barbituric acid or its *N*-alkyl derivatives with acetic anhydride [3].

Hybrid chalcones with a pyrimidine fragment were synthesized by the condensation of 5-acyl derivatives of barbituric and thiobarbituric acids with benzaldehyde and 4-hydroxy-, 2-hydroxy, 3-methoxy-, 4-chloro-, and 3-nitrobenzaldehydes [4] and tested for in vitro antimicrobial activity against three bacterial strains: one gram-

positive (*Bacillus subtilis* MTCC 441), two gram-negative (*E. coli* MTCC 443 and *P. aeruginosa* MTCC 1688), and one fungal strain (*C. albicans* MTCC 227). The dependence of the antimicrobial activity of chalcones on the electronic nature of the substituents and their position in them was analyzed to establish that chalcones containing a thioxo group are more active than chalcones containing an oxo group.

The reactions of barbituric acid with chalcones under various conditions are also well known [5–7].

RESULTS AND DISCUSSION

With a view to preparing new hybrid chalcones with a pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione fragment, we studied the condensation of 5-acetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**1**) with 4-fluoro- (**2a**), 3-fluoro- (**2b**), and 2-methoxy-3,5-dichlorobenzaldehydes (**2c**), as well as with methyl *N*-(4-formyl-2-oxo-2*H*-chromen-7-yl)carbamate (**2d**) in butan-1-ol under reflux for 4 h in the presence of piperidine and glacial acetic acid. Based on the IR and ^{1}H NMR spectra of the resulting products, they were assigned the structures 5-[(*E*)-3-aryl-2-propenoyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones **3a**–**3c** and methyl *N*-2-oxo-4-[(*E*)-3-oxo-3-(2,4,6-trioxohexahydropyrimidin-5-yl)-1-propenyl]-2*H*-chromen-7-ylcarbamate (**3d**) (Scheme 1). The yields of compounds **3a**–**3d** were quite good.

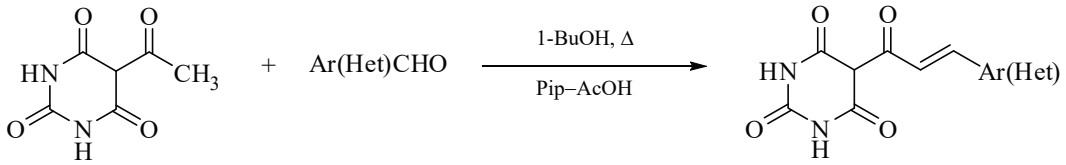
The IR spectra of compounds **3a**–**3d** contain absorption bands at 3550–3439 and 1690–1695 cm^{-1} assignable to stretching vibrations of the NH and C=O groups, respectively.

In the ^{1}H NMR spectra of chalcones **3a**–**3d**, the protons of the double bond conjugated with the carbonyl group appear as two doublets at 6.81–7.23 and 8.15–8.60 ppm with coupling constants of 22–23 Hz, which indicates the *E* configuration of the compounds. The C^{5}H proton of the barbituric acid fragment gives a singlet at 4.14–4.21 ppm, and the NH protons give two downfield singlet signals at 10.61–11.73 ppm.

To obtain chalcones with potential antioxidant activity, we studied the condensation of compound **1** with syringaldehyde (**4a**) and vanillin (**4b**) under the same conditions. Attempted base-catalyzed synthesis of such hybrid chalcones with a pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione fragment were unsuccessful, and to accomplish these condensations, we resorted to acid catalysis, because we had previously successfully used for the synthesis of hydroxy-substituted chalcones with a carbamate function [8].

It was established that the condensation of 5-acetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**1**) with aldehydes **4a** and **4b** in dioxane at room temperature in the presence of BF_3OEt_2 (Scheme 2) resulted in the formation of

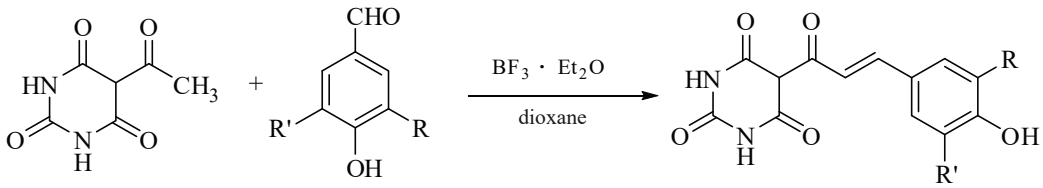
Scheme 1.



1 **2a–2d** **3a–3d**

2, 3: Ar = 4-FC_6H_4 (**a**); 3-FC_6H_4 (**b**); 2-MeO-3,5$Cl_2C_6H_3$ (**c**); Het = 7-(methoxycarbonylamino)-2-oxo-2*H*-chromen-4-yl (**d**).

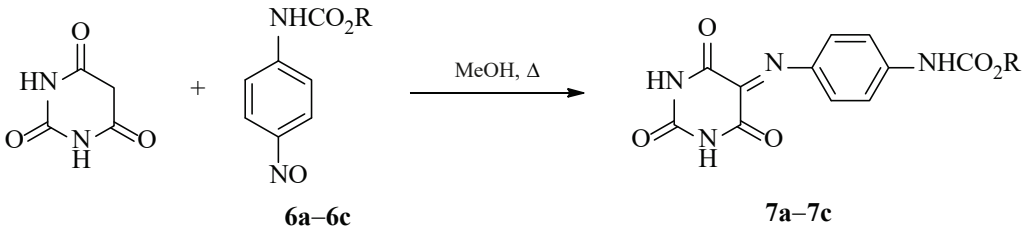
Scheme 2.



1 **4a, 4b** **5a, 5b**

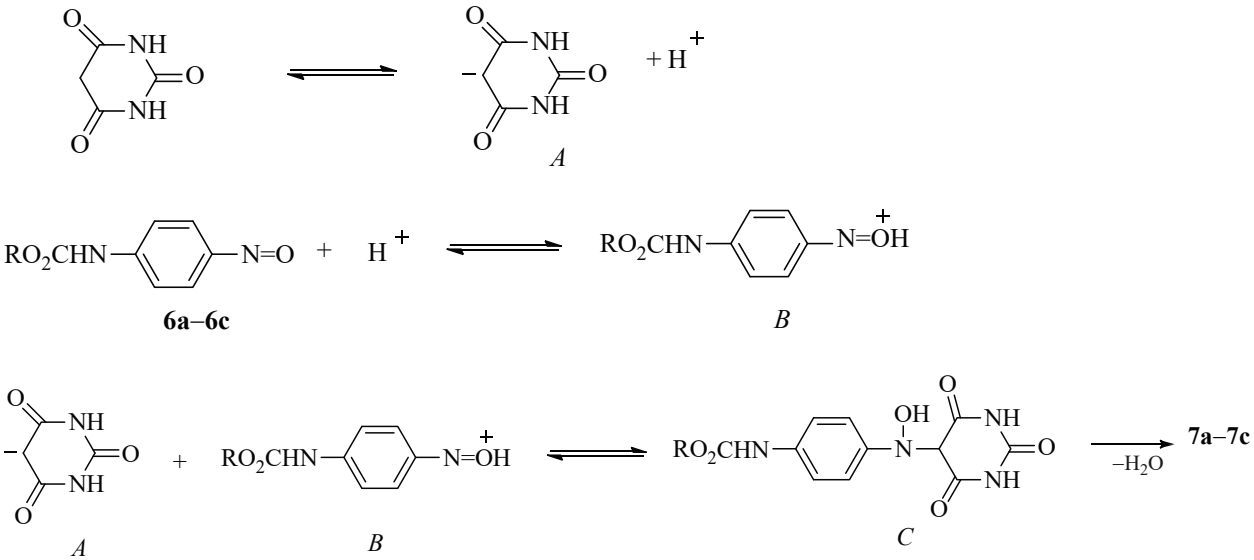
4, **5**, R = R' = OMe (**a**), R = OMe, R' = H (**b**).

Scheme 3.



6, **7**, R = Me (**a**), $PhCH_2$ (**b**), *cyclo*-C_6H_{11} (**c**).

Scheme 4.



chalcones **5a** and **5b**, respectively, whose structure was confirmed by IR and ^{1}H NMR spectroscopy.

Similarly to compounds **3a**–**3d**, chalconoids **5a** and **5b** exist in the *E* configuration (*J* 20–21 Hz). The ^{1}H NMR spectra of compounds **5a** and **5b** show, along with other signals, singlet signals of the phenolic hydroxyl at 7.14 and 7.23 ppm, respectively.

As known, the 5-CH_2 group of barbituric acid has CH acidity due to its location between two electron-acceptor carbonyl groups. It is also known that these acids and their *N*-alkyl and *N*-aryl derivatives undergo facile condensation with various aromatic and heterocyclic aldehydes. At the same time, the nitroso group of aromatic *C*-nitroso compounds can exhibit carbonyl activity and act as a kind of nitrogen analog of the carbonyl group.

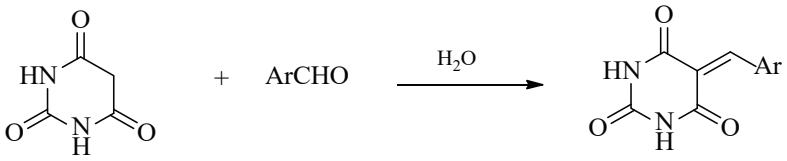
In this regard, we studied the condensation of pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione with methyl (**6a**), benzyl (**6b**), and cyclohexyl *N*-(4-nitrosophenyl)carbamates (**6c**) [9] in chloroform, DMF, ethanol, methanol, or DMF–water mixture (2 : 1) under reflux, leading to the formation of imines **7a**–**7c**, respectively (Scheme 3). It was found that the most optimal reaction conditions involved refluxing an equimolar mixture of reagents in methanol for 40 min.

The synthesized compounds are red-orange crystals. The IR spectra of compounds **7a–7c**, unlike those of the starting compounds, show an absorption band in the range 1638–1640 cm^{-1}, assignable to stretching vibrations of the C=N bond.

In the ^{1}H NMR spectra of imines **7a–7c** display, along with other proton signals, doublets of the benzene ring protons in the region of 7.53 and 7.89 ppm with a coupling constant of 8.6 Hz.

The plausible mechanism of the condensation reaction is shown in Scheme 4.

Scheme 5.



4a, 4b, 8, 9 **10–13**

Ar = 4-OH-3,5-$(OMe)_2C_6H_2$ (**4a**, **10**), 4-OH-3-$OMeC_6H_3$ (**4b**, **11**), 4-OHC_6H_4 (**8**, **12**), 2,4-$(OH)_2C_6H_3$ (**9**, **13**).

The reaction probably begins with deprotonation of barbituric acid to form anion *A*, followed by protonation of the oxygen atom of the nitroso group in compounds **6a**–**6c** to form intermediate *B*; the subsequent reaction between intermediates *A* and *B* leads to intermediate *C*, which is stabilized by elimination of a water molecule to form imines **7a**–**7c**.

Shi et al. [10] and Ali Bamanie et al. [11] proposed a method for the synthesis of 5-arylidene derivatives of barbituric and thiobarbituric acids, which involves condensation with benzaldehyde and 3,4-dimethoxy- and 3,4,5-trimethoxybenzaldehydes under stirring for 10–15 min in water at room temperature in the presence of monoethanolamine or 50% aqueous TsONa as catalysts. Similar transformations have been also accomplished in the absence of a catalyst in water under heating and at room temperature [12, 13], in alcohols [14, 15], and in water containing DABCO-based ionic liquids [16]. Some 5-arylidene derivatives were prepared by mechanochemical synthesis using H_2NSO_3H or sodium acetate as catalysts [17, 18]. The preparation of 5-arylidene derivatives of barbituric acid under MW irradiation in solvent-free conditions was reported [19–21]. The following aldehydes were introduced into this transformation: 3,4-methylenedioxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde, 4-(dimethylamino)benzaldehyde, 4-chlorobenzaldehyde, thiophene-2-carbaldehyde, furfural, 3-(2-furyl)acrolein, and 5-nitrofuran-2-carbaldehyde.

In order to synthesize new 5-arylidene pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione derivatives with potential antioxidant activity, we studied the condensation of barbituric acid with 4-hydroxy-3,5-dimethoxy- (**4a**), 4-hydroxy-3-methoxy- (**4b**), 4-hydroxy- (**8**), and 2,4-dihydroxy benzaldehydes (**9**) in water at room temperature under vigorous stirring. It was found that the reaction of equimolar amounts of the reagents provides corresponding 5-arylidenebarbituric acid derivatives **10**–**13** in high yields within 35 min (Scheme 5).

The structure of compounds **10**–**13** was confirmed by IR and 1H NMR spectroscopy. The ^{1}H NMR spectra of compounds **10**–**13** contain a singlet signal of the olefin bond proton at 8.27–8.30 ppm. The IR spectra contain absorption bands in the region of 3550–3435 cm^{-1} due to stretching vibrations of the NH groups, as well as absorption bands at 1710–1712 and 1680–1698 cm^{-1} due to stretching vibrations of the C=O and NH–CO–NH bonds, respectively.

Compound **10** was further functionalized via its condensation with aminoguanidine bicarbonate in methanol in the presence of sodium methoxide to obtain 7-hydrazinyl-5-(4-hydroxy-3,5-dimethoxyphenyl)pyrimido-[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**14**) (Scheme 6).

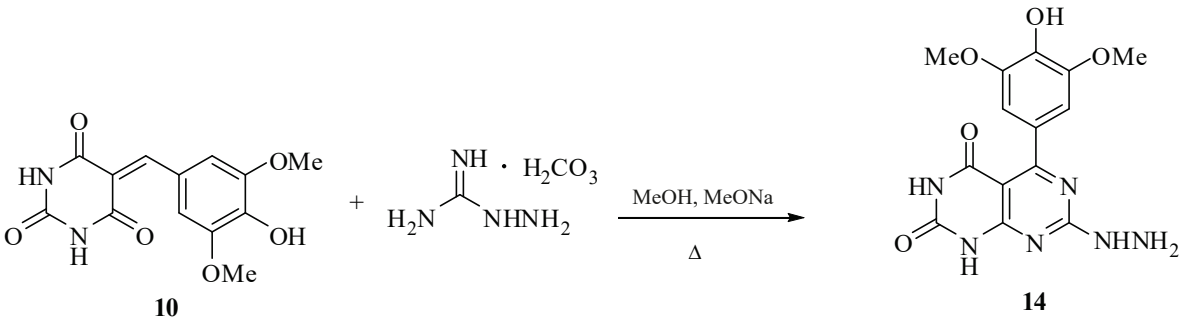
The structure of compound **14** was confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum, along with other carbon signals, shows signals of the atoms C^5 and C^7 atoms at 167.40 and 165.87 ppm, respectively.

The formation of compound **14** probably occurs by the mechanism presented in Scheme 7.

The 1,4-addition of a nucleophile to 5-arylidene derivative **10** leads to the formation of intermediate *D*, which is in equilibrium with tautomer *E*, the elimination of water from which gives 7-hydrazinyl-5-(4-hydroxy-3,5-dimethoxyphenyl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**14**).

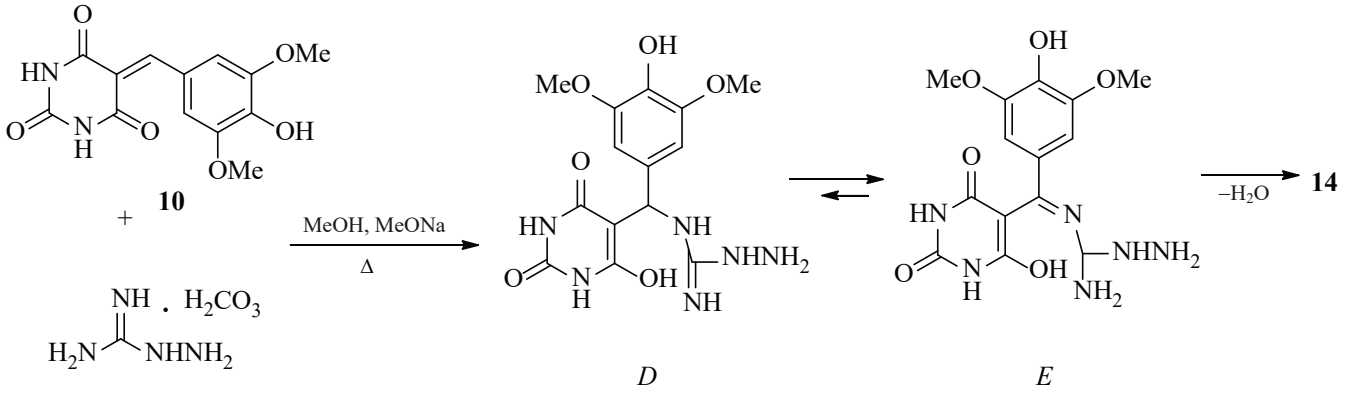
It is known that the MW-assisted one-step cyclocondensation of barbituric acid with arylidene acetophenones in glacial acetic acid in the presence of P_2O_5 or in ethanol or acetic acid under reflux [5, 6, 22] gives rise to dioxo-5*H*-pyrano[2,3-*d*]pyrimidines or biologically active barbitones. To expand the range of such deriva-

Scheme 6.



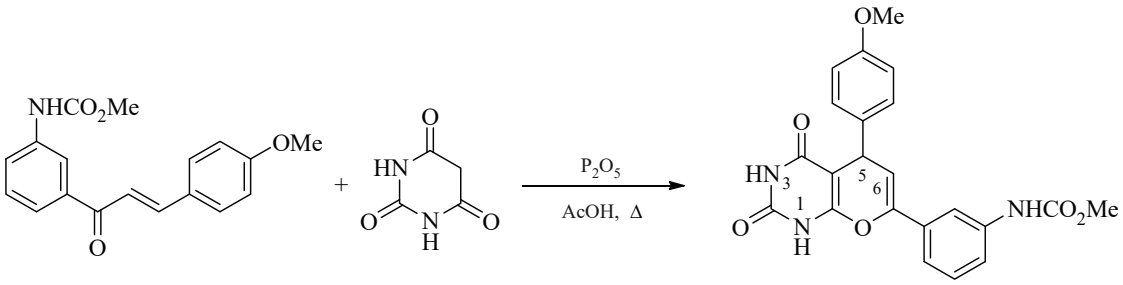
10 **14**

Scheme 7.



10 *D* *E* **14**

Scheme 8.



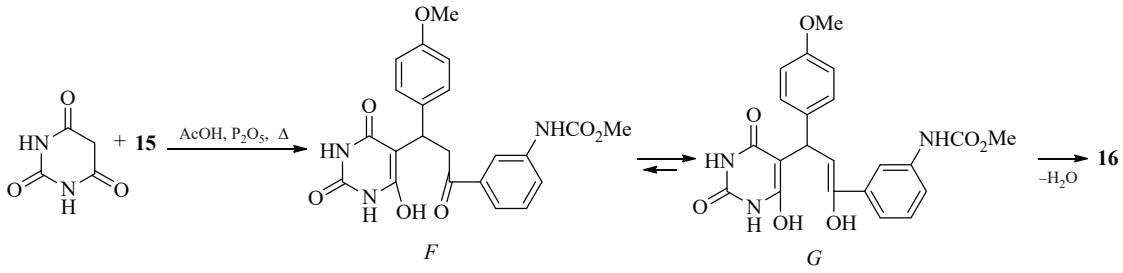
15 **16**

tives, we studied the condensation of pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione with methyl *N*-{3-[(*E*)-3-(4-methoxyphenyl)-2-propenoyl]phenyl}carbamate (**15**) by refluxing for 8 h in glacial AcOH in the presence of P_2O_5. It was found that the cyclocondensation reaction results in the formation of methyl {3-[5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-7-yl]phenyl}carbamate (**16**) (Scheme 8).

The structure of compound **16** was confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy. The IR spectrum contains absorption bands at 3550, 3310 and 1724, 1682 cm^{-1}, associated with stretching vibrations of the NH and C=O groups, respectively. The ^{1}H NMR spectrum of compound **16**, along with other proton signals, displays doublets at 4.40 and 5.42 ppm (*J* 4 Hz) due to C^5 and C^6 atoms, respectively. In the ^{13}C NMR spectrum, the signals of the C^5 and C^6 atoms of the pyran ring appear in the region of 34.92 and 105.48 ppm, which is consistent with published spectral data for compounds with a similar structure [7].

The plausible mechanism of 2*H*-pyrano[2,3-*d*]pyrimidine derivative **16** is shown in Scheme 9.

Scheme 9.



The addition of barbituric acid to the double bond of chalcone **15** leads to the formation of adduct *F*, which undergoes enolization to form intermediate *G*, whose cyclocondensation yields compound **16**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX 500 spectrometer at 500 and 126 MHz, respectively, in DMSO-d_6. The ^{13}C NMR spectra were measured with complete proton decoupling. The IR spectra were measured on an Infra LUMFT-02 FTIR spectrophotometer (in the range of 4000–400 cm^{-1} in KBr. The purity of the products was controlled by TLC on Chemapol Silufol UV-254 plates, visualization in iodine vapor. The elemental analyses were obtained on a Perkin–Elmer Series II 2400 analyzer. Commercial reagents from Aldrich and Alfa Aesar) were used in the work. 5-Acetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione was obtained by the procedure in [23].

5-[(*E*)-3-(4-Fluorophenyl)prop-2-enoyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3a). A mixture of 0.204 g (1.2 mmol) of 5-acetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**1**), 0.13 mL (1.2 mmol) of 4-fluorobenzaldehyde (**2a**) in 5 mL of butan-1-ol was heated to reflux, cooled to room temperature, 0.3 mL of piperidine and 0.3 mL of glacial acetic acid were then added, and the resulting mixture was refluxed for 4 h. The solvent was removed, the residue was dissolved in ethanol (5 mL) and poured into ice water, and the precipitate that formed was filtered off and recrystallized from 60% ethanol. Yield 0.28 g (86%), orange crystals, mp 155–157°C. IR spectrum, ν, cm^{-1}: 3550–3437 (NH), 1695 (C=O), 1612, 1575 (C–C$_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 4.19 s (1H, H^5), 7.03 s (1H$_{arom.}$, H^2), 7.15 d (1H, (CO)C**H**=CHAr, *J* 23 Hz), 8.15 d (1H, (CO)CH=C**H**Ar, *J* 23 Hz), 7.22–7.30 m (2H$_{arom.}$), 10.98 s (1H, NH), 11.73 s (1H, NH). Found, %: C 56.39; H 3.33; N 9.95. $C_{13}H_9FN_2O_4$. Calculated, %: C 56.52; H 3.26; N 10.15.

5-[(*E*)-3-(3-Fluorophenyl)prop-2-enoyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3b) was obtained similarly to compound **3a** by the reaction of 0.204 g (1.2 mmol) of compound **1** and 0.127 mL (1.2 mmol) of 3-fluorobenzaldehyde (**2b**). Yield 0.278 g (84%), yellow crystals, mp 122–125°C. IR spectrum, ν, cm^{-1}: 3550–3439 (NH), 1692 (C=O), 1611, 1575, 1565 (C–C$_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 4.21 s (1H, H^5), 6.98 d (2H$_{arom.}$, *J* 8.8 Hz), 7.18–7.25 m (3H, 2H$_{arom.}$, (CO)C**H**=CHAr), 8.38 d (1H, (CO)CH=C**H**Ar, *J* 22 Hz), 10.97 s (1H, 1NH), 11.70 (1H, NH). Found, %: C 56.43; H 3.05; N 9.98. $C_{13}H_9FN_2O_4$. Calculated, %: C 56.52; H 3.26; N 10.15.

5-[(*E*)-3-(3,5-Dichloro-2-methoxyphenyl)prop-2-enoyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3c) was obtained similarly to compound **3a** by the reaction of 0.204 g (1.2 mmol) of compound **1** and 0.246 g (1.2 mmol) of 2-methoxy-3,5-dichlorobenzaldehyde (**2c**). Yield 0.38 g (88%), light yellow crystals, mp 249–252°C. IR spectrum, ν, cm^{-1}: 35550–3438 (NH), 1690 (C=O), 1615, 1575 (C–C$_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 3.87 s (3H, OMe), 4.21 s (1H, H^5), 6.61 s (1H$_{arom.}$), 6.87 s (1H$_{arom.}$), 7.23 d (1H, (CO)C**H**=CHAr, *J* 23 Hz), 8.44 d (1H, (CO)CH=C**H**Ar, *J* 23 Hz), 10.61 s (1H, 1NH), 10.85 s (1H, NH). Found, %: C 46.82; H 2.63; N 7.64. $C_{14}H_{10}Cl_2N_2O_5$. Calculated, %: C 47.06; H 2.80; N 7.84.

Methyl *N*-{2-oxo-4-[(*E*)-3-oxo-3-(2,4,6-trioxohexahydropyrimidin-5-yl)prop-1-enyl]-2*H*-chtomen-7-yl}carbamate (3d) was obtained similarly to compound **3a** by the reaction of 0.204 g (1.2 mmol) of compound **1** and 0.296 g (1.2 mmol) of methyl *N*-(4-formyl-2-oxo-2*H*-chtomen-7-yl)carbamate (**2d**) [24]. Yield 0.397 g (83%), dark yellow crystals, mp 99–101°C. IR spectrum, ν, cm^{-1}: 3550–3439, 3315 (NH), 1710, 1690 (C=O), 1612, 1575 (C–C$_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO**Me**), 4.14 s (1H, H^5), 6.61 s (1H, chromene H^3), 6.81 d (1H, (CO)

C**H**=CHAr, *J* 22 Hz), 7.20 d (1H, chromene H^6, *J* 8.2 Hz), 7.60 s (1H, chromene H^8), 7.75 d (1H, chromene H^5, *J* 8.2 Hz), 8.60 d (1H, (CO)CH=C**H**Ar, *J* 22 Hz), 9.65 br s (1H, N**H**CO_2Me), 10.65 s (1H, 1NH), 10.97 (1H, NH). Found, %: C 53.89; H 3.14; N 10.36. $C_{18}H_{13}N_3O_8$. Calculated, %: C 54.14; H 3.26; N 10.53.

5-[(*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-prop-2-enoyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5a). A mixture of 0.34 g (2 mmol) of 5-acetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trionea (**1**), 0.364 g (2 mmol) of syringaldehyde (**4a**), 2 mL of anhydrous dioxane, and 0.2 mL of BF_3OEt_2 was stirred for 48 h at room temperature, and then diluted with 25 mL of chloroform, washed with water (3 × 50 mL), the organic layer was dried with anhydrous Na_2SO_4, the solvent was removed, and the crystalline residue was recrystallized from methanol. Yield 0.508 g (87%), yellow crystals, mp 100–103°C. IR spectrum, ν, cm^{-1}: 3550–3437 (NH), 3261 (Ar-OH), 1687 (C=O), 1610, 1575, 1565 (C–$C_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 3.89 s (6H, 2OMe), 4.20 s (1H, H^5), 6.47 s (2$H_{arom.}$), 7.25 d (1H, (CO)C**H**=CHAr, *J* 20 Hz), 8.12 d (1H, (CO)CH=C**H**Ar, *J* 20 Hz), 9.20 s (1H, OH), 10.55 s (1H, NH), 10.69 s (1H, NH). Found, %: C 53.75; H 4.01; N 8.38. $C_{15}H_{14}N_2O_7$. Calculated, %: C 53.89; H 4.19; N 8.38.

5-[(*E*)-3-(4-Hydroxy-3-methoxyphenyl)prop-2-enoyl]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5b) was obtained similarly to compound **5a** by the reaction of 0.34 g (2 mmol) of compound **1** and 0.304 g (2 mmol) of vanillin (**4b**). Yield 0.445 g (85%), yellow crystals, mp 76–77°C. IR spectrum, ν, cm^{-1}: 3550–3435 (NH), 3260 (Ar-OH), 1685 (C=O), 1610, 1575 (C–$C_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 3.82 s (3H, OMe), 4.21 s (1H, H^5), 6.70 s (1$H_{arom.}$), 6.76 d (1$H_{arom.}$, *J* 8.1 Hz), 6.90 d (1$H_{arom.}$, *J* 8.1 Hz), 7.18 d (1H, (CO)C**H**=CHAr, *J* 21 Hz), 8.15 d (1H, (CO)CH=C**H**Ar, *J* 21 Hz), 9.14 s (1H, OH), 10.52 s (1H, NH), 10.70 s (1H, NH). Found, %: C 55.13; H 3.64; N 8.97. $C_{14}H_{12}N_2O_6$. Calculated, %: C 55.26; H 3.95; N 9.21.

Methyl {4-[(2,4,6-trioxotetrahydropyrimidin-5(2*H*)-ylidene)amino]phenyl}carbamate (7a). A mixture of 0.213 g (1.66 mmol) of barbituric acid and 0.3 g (1.66 mol) of methyl *N*-(4-nitrosophenyl)carbamate (**6a**) in 10 mL of methanol was refluxed for 40 min, cooled, and diluted with 10 mL of diethyl ether. The precipitate that formed was filtered off, dried in air, and recrystallized from ethanol. Yield 0.42 g (87%), red orange crystals, mp 185–187°C (decomp.). IR spectrum, ν, cm^{-1}: 3550–3440, 3310 (NH), 1775, 1710 (C=O), 1640 (C=N), 1610, 1575 (C–$C_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 3.70 s (3H, NHCO$_2$**Me**), 7.53 d (2H, $H_{arom.}$, *J* 8.6 Hz), 7.88 d (2H, $H_{arom.}$, *J* 8.6 Hz), 9.86 s (1H, N**H**CO_2Me), 10.66 s (1H, NH), 10.88 s (1H, NH). Found, %: C 49.48; H 3.04; N 19.18. $C_{12}H_{10}N_4O_5$. Calculated, %: C 49.66; H 3.45; N 19.31.

Benzyl {4-[(2,4,6-trioxotetrahydropyrimidin-5(2*H*)-ylidene)amino]phenyl}carbamate (7b) was prepared similarly to compound **7a** by the reaction of 0.213 g (1.66 mmol) of barbituric acid and 0.425 g (1.66 mmol) of benzyl *N*-(4-nitrosophenyl)carbamate (**6b**). Yield 0.51 g (83%), red orange crystals, mp 180–182°C (decomp.) (from ethanol). IR spectrum, ν, cm^{-1}: 3550–3448, 3312 (NH), 1775, 1710 (C=O), 1638 (C=N), 1610, 1574 (C–$C_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 5.20 s (2H, OCH_2), 7.29–7.43 m (5H, $H_{arom.}$), 7.51 d (2H, $H_{arom.}$, *J* 8.7 Hz), 7.87 d (2H, $H_{arom.}$, *J* 8.7 Hz), 9.84 s (1H, N**H**CO_2CH_2Ph), 10.66 s (1H, NH), 10.89 s (1H, NH). Found, %: C 58.57; H 3.44; N 15.05. $C_{18}H_{14}N_4O_5$.Calculated, %: C 59.02; H 3.83; N 15.30.

Cyclohexyl {4-[(2,4,6-trioxotetrahydropyrimidin-5(2*H*)-ylidene)amino]phenyl}carbamate (7c) was prepared similarly to compound **7a** by the reaction of 0.213 g (1.66 mmol) of barbituric acid and 0.41 g (1.66 mmol) of cyclohexyl *N*-(4-nitrosophenyl)carbamate (**6c**). Yield 0.49 g (83%), red orange crystals, mp 225–230°C (decomp.) (from ethanol). IR spectrum, ν, cm^{-1}: 3550–3450, 3310 (NH), 1775, 1710 (C=O), 1640 (C=N), 1610, 1570 (C–$C_{arom.}$). ^{1}H NMR spectrum, δ, ppm: 1.12–1.47 m (6H, cyclohexane CH_2, 2.20–2.28 m (2H, cyclohexane CH_2), 2.37–2.43 (2H, cyclohexane CH_2), 4.92–4.97 m (1H, cyclohexane CH), 7.52 d (2$H_{arom.}$, *J* 8.7 Hz), 7.89 d (2$H_{arom.}$, *J* 8.7 Hz), 9.83 s (1H, N**H**$CO_2C_6H_{11}$), 10.67 s (1H, NH), 10.88 s (1H, NH). Found, %: C 56.63; H 4.98; N 15.42. $C_{17}H_{18}N_4O_5$. Calculated, %: C 56.98; H 5.03; N 15.64.

5-(4-Hydroxy-3,5-dimethoxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10). 4-Hydroxy-3,5-dimethoxybenzaldehyde (**4a**), 1.82 g (0.01 mol), was added to a vigorously stirred solution of 1.48 g (0.01 mol) of barbituric acid in 30 mL of water, and the resulting mixture was stirred for 35 min at room temperature. The resulting product was filtered off and washed with water (100 mL). Yield 2.83 g (97%), yellow crystals. Decom-

position point >350°C (from DMF). IR spectrum, ν, cm^{-1}: 3550–3435 (NH), 3260 (Ar-OH), 1710, 1688 (C=O), 1625 (C=C), 1610, 1575, 1565 (C–$C_{arom.}$). ^1H NMR spectrum, δ, ppm: 3.90 s (6H, $2OCH_3$), 6.80 s ($2H_{arom.}$), 8.25 s (1H, CH), 9.22 s (1H, OH), 11.18 s (1H, NH), 11.30 s (1H, NH). Found, %: C 53.37; H 3.81; N 9.37. $C_{13}H_{12}N_2O_6$. Calculated, %: C 53.43; H 4.11; N 9.59.

5-(4-Hydroxy-3-methoxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (11) was prepared similarly to compound **10** by the reaction of 1.48 g (0.01 mol) of barbituric acid and 1.52 g (0.01 mol) of vanillin aldehyde (**4b**). Yield 2.49 g (95%), bright yellow crystals, mp 309–313°C (313°C [25]) (from dioxane). IR spectrum, ν, cm^{-1}: 3550–3435 (NH), 3261 (Ar–OH), 1712, 1698 (C=O), 1625 (C=C), 1610, 1575 (C–$C_{arom.}$). ^1H NMR spectrum, δ, ppm: 3.89 s (3H, OCH_3), 6.92 d ($1H_{arom.}$, *J* 8.1 Hz), 7.77 d ($1H_{arom.}$, *J* 8.1 Hz), 8.30 s (1H, CH), 8.56 s ($1H_{arom.}$), 9.26 br s (1H, OH), 10.11 br s (1H, NH), 11.21 br s (1H, NH). Found, %: C 54.69; H 3.67; N 10.55. $C_{12}H_{10}N_2O_5$. Calculated, %: C 54.96; H 3.82; N 10.69.

5-(4-Hydroxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**12**) was prepared similarly to compound **10** by the reaction of 1.48 g (0.01 mol) of barbituric acid and 1.22 g (0.01 mol) of 4-hydroxybenzaldehyde (**8**). Yield 2.25 g (97%), golden yellow crystals, mp 299–301°C (>300°C [25]) (from ethanol). IR spectrum, ν, cm^{-1}: 3550–3435 (NH), 3260 (Ar–OH), 1712, 1697 (C=O), 1625 (C=C), 1610, 1575 (C–$C_{arom.}$). ^1H NMR spectrum, δ, ppm: 6.89 d ($2H_{arom.}$, *J* 8.7 Hz), 8.29 s (1H, CH), 8.34 d ($2H_{arom.}$, *J* 8.7 Hz), 10.01 br s (1H, NH), 10.54 br s (1H, OH), 11.30 br s (1H, NH). Found, %: C 57.01; H 3.34; N 11.86. $C_{11}H_8N_2O_4$. Calculated, %: C 56.90; H 3.45; N 12.07.

5-(2,4-Dihydroxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**13**) was prepared similarly to compound **10** by the reaction of 1.48 g (0.01 mol) of barbituric acid and 1.38 g (0.01 mol) of 2,4-dihydroxybenzaldehyde (**9**). Yield 2.36 g (95%), yellow crystals (decomp.> 240°C. IR spectrum, ν, cm^{-1}: 3550–3435 (NH), 3259 (Ar-OH), 1710, 1680 (C=O), 1625 (C=C), 1616, 1575 (C–$C_{arom.}$). ^1H NMR spectrum, δ, ppm: 6.87 d ($1H_{arom.}$, *J* 8.7 Hz), 7.03 s ($1H_{arom.}$), 7.14 d ($1H_{arom.}$, *J* 8.7 Hz), 8.27 s (1H, CH), 10.11 br s (1H, NH), 10.54 br s (2H, 2OH), 11.28 br s (1H, NH). Found, %: C 52.95; H 3.17; N 11.34. $C_{11}H_8N_2O_5$. Calculated, %: C 53.23; H 3.23; N 11.29.

7-Hydrazinyl-5-(4-hydroxy-3,5-dimethoxyphenyl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (14). Sodium, 0.12 g (5 mmol), was added to 25 mL of methanol. Upon completion of the reaction 0.68 g (5 mmol) of aminoguanidine bicarbonate was added, the mixture was refluxed for 1 h, cooled, and 1.46 g (5 mmol) of 5-[(4-hydroxy-3,5-dimethoxyphenyl) methylene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**10**) was added. The resulting mixture was refluxed for 5 h and then poured onto ice and acidified with glacial acetic acid. The precipitate that formed was filtered off, dried in air, and recrystallized from an ethanol–dioxane mixture, 1 : 1. Yield 1.107 g (64%), light yellow crystals, mp 130–132°C. IR spectrum, ν, cm^{-1}: 3550–3310 (NH, NH_2), 3262 (Ar-OH), 1610, 1570 (C–$C_{arom.}$). ^1H NMR spectrum, δ, ppm: 3.72 s (6H, $2OCH_3$), 4.35–4.40 m (4H, OH, NH-NH_2), 7.29 s ($2H_{arom.}$), 9.12 s (1H, NH), 13.32 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 56.35 (2OMe), 102.43 (C^9), 145.59 (NH-CO-NH), 161.96 (NHCO), 167.40 (C^5), 114.25, 128.09, 142.64, 154.83 (C_{Ar}), 165.87 (C^7). Found, %: C 48.39; H 3.76; N 14.14. $C_{14}H_{14}N_6O_5$. Calculated, %: C 48.56; H 4.05; N 24.28.

Methyl {3-[5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-7-yl]phenyl}carbamate (16). A mixture of 0.64 g (5 mmol) of barbituric acid, 1.555 g (5 mmol) of methyl *N*-{3-[(*E*)-3-(4-methoxyphenyl)prop-2-enoyl]phenyl}-carbamate (**15**), and 1.5 g of P_2O_5 in 15 mL of glacial acetic acid was refluxed for 8 h, cooled, and treated with 50 g of crushed ice. The precipitate that formed was filtered off, washed with water, dried in air, and recrystallized from ethanol. Yield 1.3 g (72%), brown crystals, mp 275–277°C. IR spectrum, ν, cm^{-1}: 3550, 3310 (NH), 1724, 1682 (C=O), 1610, 1565 (C–$C_{arom.}$). ^1H NMR spectrum, δ, ppm: 3.62 s (3H, OCH_3), 3.71 s (3H, $NHCO_2$**Me**), 4.40 d (1H, H^5, *J* 4 Hz), 5.42 d (1H, H^6, *J* 4 Hz), 6.54 d ($2H_{arom.}$, *J* 8.9 Hz), 6.95 d ($1H_{arom.}$, *J* 8.9 Hz), 7.08 d ($1H_{arom.}$, *J* 8.9 Hz), 7.34 t ($1H_{arom.}$, *J* 7.6 Hz), 7.48 d ($1H_{arom.}$, *J* 7.6 Hz), 7.63 d ($1H_{arom.}$, *J* 7.6 Hz), 7.76 s ($1H_{arom.}$), 9.54 br s (1H, N**H**CO_2Me), 10.02 br s (1H, NH), 11.06 br s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 34.92 (C^5), 52.58 ($NHCO_2$**Me**), 55.69 (OMe), 84.15 (C^9), 105.48 (C^6), 113.65, 118.21. 122.32, 122.79, 126.21, 128.35, 129.63, 134.72, 138.01, 157.38 (C_{Ar}), 141.38 (C^7), 146.02 (NH-CO-NH), 154.87

(NH**C**O_2Me), 161.87 (NHCO), 165.27 (C^{10}). Found, %: C 62.64; H 4.37; N 9.77. $C_{22}H_{19}N_3O_6$. Calculated, %: C 62.71; H 4.51; N 9.98.

CONCLUSION

New hybrid chalcones with pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione fragments were synthesized on the basis of 5-acetylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione. Alkyl {4-[(2,4,6-trioxotetrahydropyrimidin-5(2*H*)-ylidene)amino]phenyl}carbamates were obtained by the condensation of pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione with alkyl *C*-nitrosophenylcarbamates in methanol. A 5-arylidene derivative with a 4-hydroxy-3,5-dimethoxyphenyl moiety and pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione were converted into 7-hydrazinyl-5-(4-hydroxy-3,5-dimethoxyphenyl)pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione and methyl {3-[5-(4-methoxyphenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]-pyrimidin-7-yl]phenyl}carbamate by the reactions with aminoguanidine bicarbonate and chalcone with a carbamate function, respectively.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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