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Proceeding Paper

Approaches to the Synthesis of New Symmetrical Bridged Bis(6-hydroxypyrimidin-4(3*H*)-ones)

Darya Mikhailovna Stepkina, Sofya Sergeevna Merkusheva, Denis Andreevich Kolesnik *, Galina Vladimirovna Ksenofontova and Igor Pavlovich Yakovlev

Department of Organic Chemistry, State Federal-Funded Educational Institution of Higher Education «Saint Petersburg State Chemical and Pharmaceutical University of the Ministry of Healthcare of the Russian Federation», Professor Popov str., 14, lit. A, 197022 St. Petersburg, Russia; darya.stepkina@spcpu.ru (D.M.S.); sofya.merkusheva@spcpu.ru (S.S.M.); galina.ksenofontova@pharminnotech.com (G.V.K.); igor.yakovlev@pharminnotech.com (I.P.Y.)

* Correspondence: denis.kolesnik@spcpu.ru

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Abstract

Introduction. The synthesis of new symmetrical bridged bis(6-hydroxypyrimidin-4(3*H*)-ones) is of significant interest in modern chemistry and pharmaceuticals. Due to their unique structure, such systems have the potential to create new drugs with improved pharmacological properties. They are widely known for their antiviral, antitumor, and antibacterial properties, making them attractive candidates for the development of new therapeutic agents. This work considers two approaches to the synthesis of new bis(6-hydroxypyrimidin-4(3*H*)-ones) with aromatic and aliphatic linkers. **Methods.** Bis(6-hydroxypyrimidin-4(3*H*)-ones) (**1a–c**), substituted with an aromatic 1,4-phenylene bridge at the 2,2′ positions, were obtained by the reaction of *N*′^{1},*N*′^{4}-diphenylbenzene-1,4-dicarboximidamide with an excess of 2-substituted malonylchlorides. The 5,5′-substituted derivatives of bis(6-hydroxypyrimidin-4(3*H*)-one) with a trimethylene bridge (**2a–c**) were obtained through the interaction of *N*-phenylimidamides and tetraethyl propane-1,1,3,3-tetracarboxylate. The structure of the synthesized compounds was confirmed using ^{1}H and ^{13}C NMR spectroscopy. **Results and Conclusions.** The yield of 2,2′-(1,4-phenylene)bis(6-hydroxy-5-substituted-3-phenylpyrimidin-4(3*H*)-ones) (**1a–c**) ranged from 34–71%. It was found that the substituent in the malonylchloride affects the yield of the products. Alkyl substituents facilitate the obtainment of target compounds with higher yields compared to the aromatic phenyl group. The yield of 5,5′-propane-1,3-diylbis(6-hydroxy-2-substituted-1-phenylpyrimidin-4(3*H*)-ones) (**2a–c**) ranged from 58–72%. It was discovered that the presence of aliphatic substituents in *N*-phenylimidamide leads to the obtainment of these compounds with higher yields compared to the use of *N*-phenylbenzocarboximidamide.

Keywords: bis(6-hydroxypyrimidin-4(3*H*)-ones); imidamides; aromatic and aliphatic linkers

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1. Introduction

Currently, the search for new biologically active compounds is receiving increasing attention. The modification of known pharmaceutical substances often leads to the

creation of more effective drugs, facilitated by their initially broad spectrum of biological activity. Known bipyrimidine derivatives exhibit a wide range of biological activities: antitumor [1], antibacterial [2], antiviral [3], antimicrobial [4], antileishmanial [5], tuberculostatic [6], anti-inflammatory [7], and analgesic [8], making them attractive candidates for the development of new therapeutic agents.

Thus, the synthesis of new bis(6-hydroxypyrimidin-4(3*H*)-ones) with linkers of varying structures is of significant interest to modern chemistry and pharmaceutics. Symmetrical systems containing bridging fragments, due to their unique structure, have the potential for creating new drug agents with improved pharmacological properties.

This work discusses two approaches to the synthesis of new symmetrical bis(6-hydroxypyrimidin-4(3*H*)-ones) with aromatic and aliphatic linkers.

2. Materials and Methods

Derivatives of bis(6-hydroxypyrimidin-4(3*H*)-one) substituted at the 2,2′-positions with a 1,4-phenylene linker (**3**) were synthesized by reacting an excess of 2-substituted propanedioyl dichlorides (**4**) with N^1,N^4-diphenylbenzene-1,4-dicarboximidamide (**3**) in boiling benzene for 15–17 h (Figure 1).

Derivatives of 5,5′-substituted bipyrimidines (**2a–c**) were obtained by fusion of *N*-substituted imidamides (**5a–c**) with tetraethyl propane-1,1,3,3-tetracarboxylate (**6**) in DMF in the presence of a catalytic amount of potassium bicarbonate for 3–6 h (Figure 1).

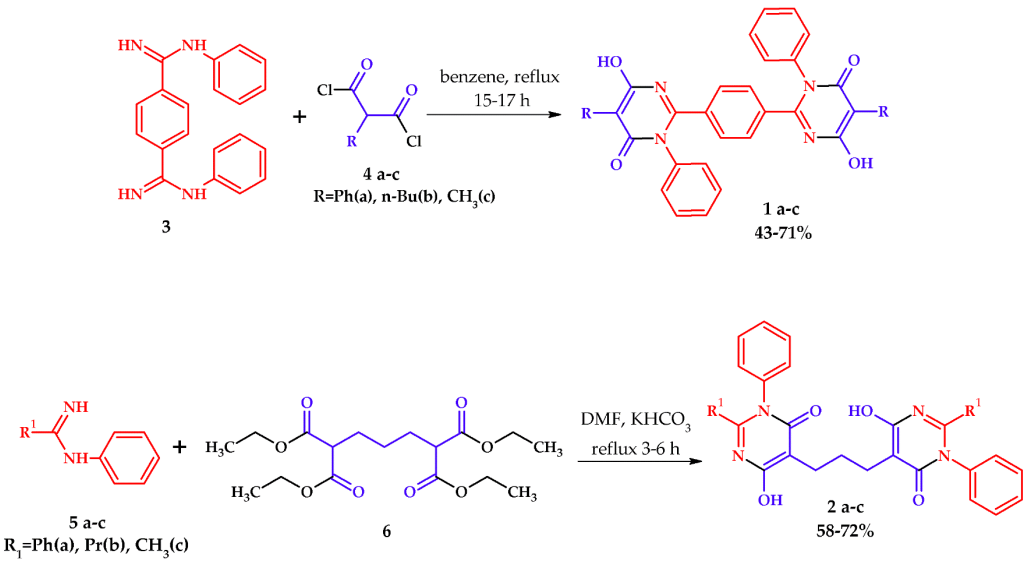

Figure 1. Synthesis of *N*-substituted bis(6-hydroxypyrimidin-4(3*H*)-ones).

Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance III (^{1}H—400 MHz, ^{13}C—100 MHz) (Bruker, Germany). Approximately 0.01 g of the sample was dissolved in an appropriate solvent, and NMR spectra were recorded. The spectral data were processed using MestReNova software version 12.0.0-20080.

3. Results and Conclusions

The yields of 2,2′-(1,4-phenylene)bis(6-hydroxy-5-substituted-3-phenylpyrimidin-4(3*H*)-ones) (**1a–c**) were 34–71% (Figure 4). It was found that the substituent in the starting malonyl chloride affects the product yield. Alkyl substituents (methyl and butyl) afforded the target compounds in higher yields compared to the aromatic phenyl substituent.

The yields of 5,5′-(propane-1,3-diyl)bis(6-hydroxy-2-substituted-1-phenylpyrimidin-4(3*H*)-ones) (**2a–c**) were 58–72% (Figure 2).

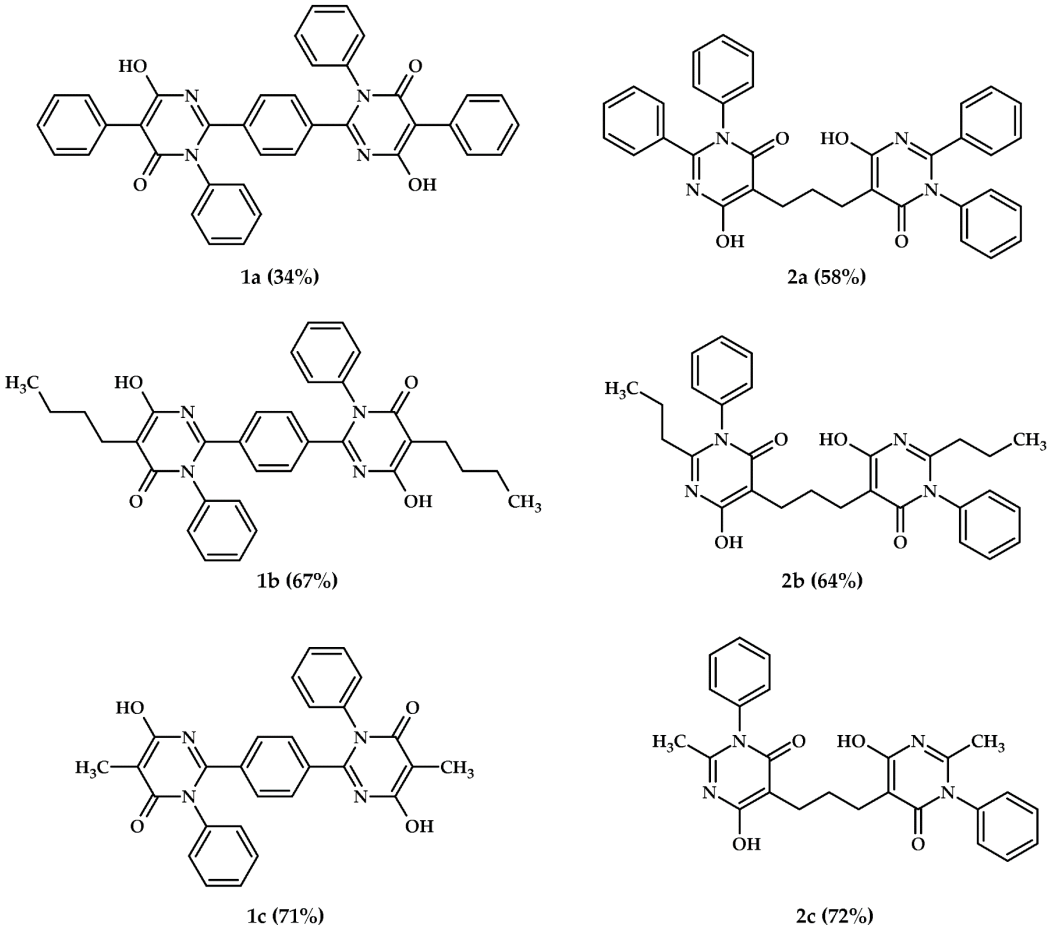

Figure 2. Structures of new bis(6-hydroxypyrimidin-4(3*H*)-ones): **1a**—2,2′-(1,4-phenylene)bis(6-hydroxy-5-phenyl-3-phenylpyrimidin-4(3*H*)-one); **1b**—2,2′-(1,4-phenylene)bis(6-hydroxy-5-butyl-3-phenylpyrimidin-4(3*H*)-one); **1c**—2,2′-(1,4-phenylene)bis(6-hydroxy-5-methyl-3-phenylpyrimidin-4(3*H*)-one); **2a**—5,5′-propane-1,3-diylbis(1,2-diphenyl-1,2-dihydropyrimidine-4,6-diol); **2b**—5,5′-propane-1,3-diylbis(1-phenyl-2-propyl-1,2-dihydropyrimidine-4,6-diol); **2c**—5,5′-propane-1,3-diylbis(2-methyl-1-phenyl-1,2-dihydropyrimidine-4,6-diol).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) of 2,2′-(1,4-phenylene)bis(6-hydroxy-5-butyl-3-phenylpyrimidin-4(3*H*)-one), δ, ppm: 0.89 (t, 6H, J = 7.28 Hz, CH_3); 1.26–1.27 (m, 8H, -CH_2-CH_2-); 2.34 (t, 4H, J = 7.28 Hz, -CH_2-CAr); 7.11–7.28 (m, 14H, CAr-H); 11.43 (br s, 2H, -OH) (Figure 3).

^{13}C NMR (100 MHz, acetone-*d*$_6$) of 2,2′-(1,4-phenylene)bis(6-hydroxy-5-butyl-3-phenylpyrimidin-4(3*H*)-one), δ, ppm: 13.45; 22.54; 53.62; 53.81; 54.00; 54.17; 68.33; 69.44; 121.55; 128.25; 128.37; 128.54; 129.36; 209.11. (Figure 4).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) of 5,5′-(propane-1,3-diyl)bis(1,2-diphenyl-1,2-dihydropyrimidine-4,6-diol), δ, ppm: 1.51 (s, 2H, -CH_2-); 2.21 (m, 2H, -CH_2-); 2.40 (m, 2H, -CH_2-); 7.15–7.59 (m, 20H, CAr-H); 11.76 (br s, 2H, -OH) (Figure 5).

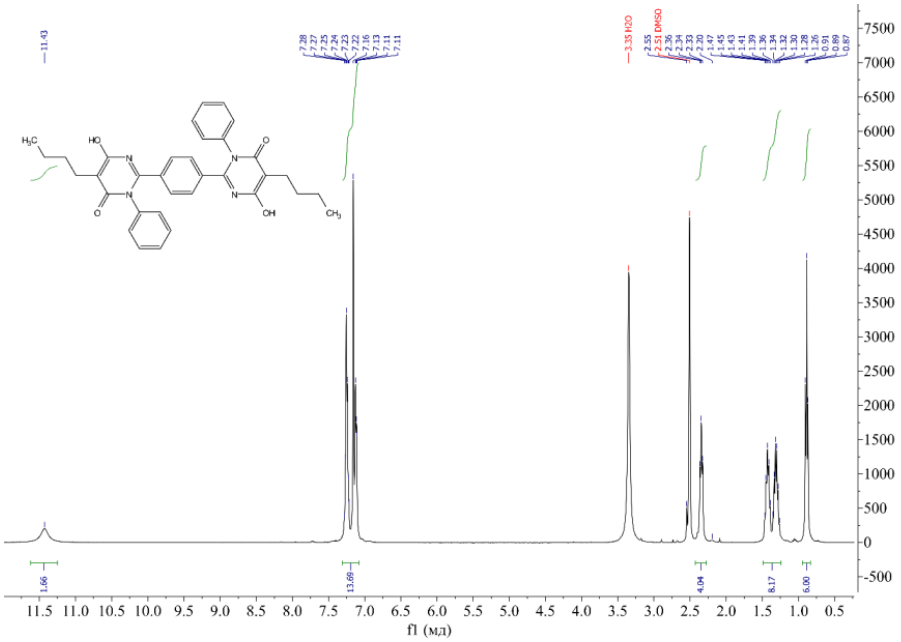

Figure 3. [1]H NMR (400 MHz, DMSO-d_6) of 2,2′-(1,4-phenylene)bis(6-hydroxy-5-butyl-3-phenylpyrimidin-4(3*H*)-one).

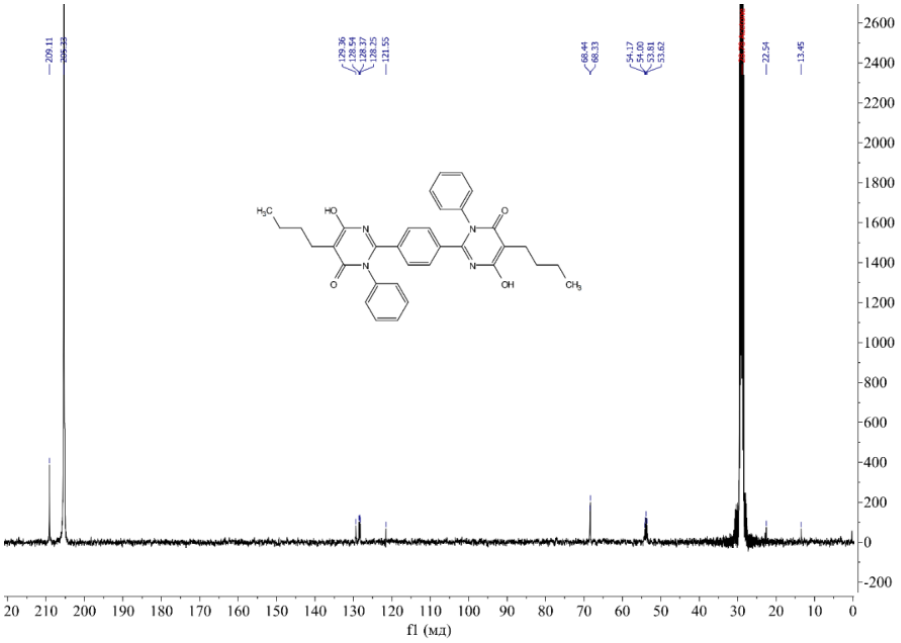

Figure 4. [13]C NMR (100 MHz, acetone-d_6) of 2,2′-(1,4-phenylene)bis(6-hydroxy-5-butyl-3-phenylpyrimidin-4(3*H*)-one).

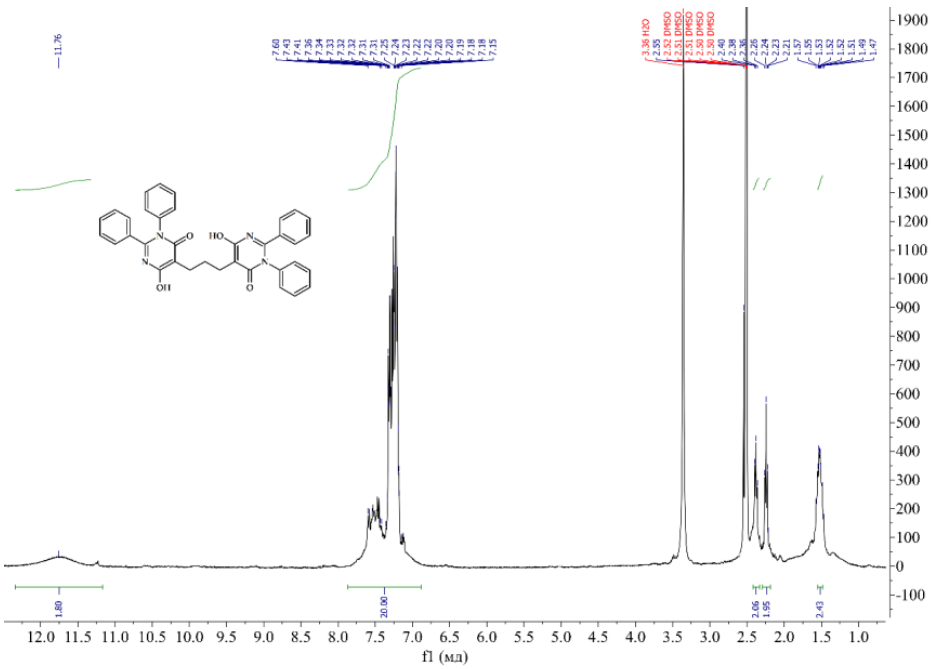

Figure 5. ^{1}H NMR (400 MHz, DMSO-d_6) of 5,5′-propane-1,3-diylbis(1,2-diphenyl-1,2-dihydropyrimidine-4,6-diol).

Thus, six new bis(6-hydroxypyrimidin-4(3*H*)-ones) with aromatic and aliphatic linkers were synthesized. It was established that the yield of the target products is influenced by the nature of the substituent in the starting malonyl chloride (**4a–c**). For the compounds with the 1,4-phenylene linker (**3**), the yield was significantly lower with an aromatic substituent due to steric factors, while higher yields were observed with aliphatic substituents. The nature of the substituent in the starting *N*-substituted benzenecarboximidamide also affected the yield of the final product for the compounds with the aliphatic bridge (**2a–c**), where both steric factors and the nucleophilicity of the imidamide played a role.

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Abbreviations

NMR	Nuclear Magnetic Resonance
DMSO	Dimethyl sulfoxide

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