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New Synthesis of 2-Aminopyrimidines by Amination of Biginelli Reaction Products — Oxadiazocines

Previously, we synthesized methanobenzo[g][1,3,5]oxadiazocines and methanonaphtho[2,3-g][1,3,5]oxadiazocines via the Biginelli reaction using thiourea with acetoacetic ester or acetylacetone and salicylaldehyde or 2-hydroxy-1-naphthaldehyde under acidic catalysis and microwave irradiation. These compounds were then subjected to alkylation reaction with ethyl bromide in the presence of potassium carbonate in dimethylformamide. Under these mild reaction conditions, possible thione-thiol tautomerism of the oxadiazocines, as well as their structural analogs of cyclic thioureas, predominantly yielded in S-alkylation products with minor amounts of N-alkylation products. Further nucleophilic substitution reactions of S-ethyl-methanobenzo[g][1,3,5]oxadiazocines and S-ethyl-methanonaphtho[2,3-g][1,3,5]oxadiazocines revealed that alongside nucleophilic substitution by morpholine, elimination of phenol or naphthol occurred, followed by aromatization of the dihydropyrimidinone ring into an aromatic pyrimidine ring, resulting in the formation of 2-morpholinyl-substituted pyrimidines. Only a few examples and multi-step syntheses for obtaining such 2-amino-substituted pyrimidines are presented in the literature. Therefore, our newly discovered method for obtaining widely demanded derivatives of 2-aminopyrimidines is presented both relevant and promising.

Keywords: 2-aminopyrimidines, Biginelli reaction, oxadiazocines, methanonaphtho[2,3-g][1,3,5]oxadiazocine, methanobenzo[g][1,3,5]oxadiazocine, thione-thiol tautomerism, alkylation, morpholine, amination.

Introduction

Many natural and synthetic biomolecules exhibit their properties due to the presence of the pyrimidine ring. This ring is a crucial structural component in substances essential for maintaining vital functions in living organisms, including vitamins, coenzymes, and uric acid. The aminopyrimidine ring is a vital building block of the nucleotide bases found in DNA and RNA, which are crucial for the proper functioning of living cells. This emphasizes the immense importance of these compounds in nature. Derivatives of 2-aminopyrimidines have a wide range of biological activities, making them a subject of great interest in organic synthesis for many years. Consequently, there is a significant interest in exploring innovative synthetic methods for their preparation [1–3].

Pyrimidine heterocycles find their main application in medicinal chemistry, primarily attributed to their potential as inhibitors of nucleic acid synthesis in infected cells or as carriers for delivering pharmacophoric groups to specific biological sites. Examples of such drugs include anticancer drugs such as Abemaciclib [4] and Imatinib [5]. 2-Aminopyrimidines are known for their diverse spectrum of activities, including anticancer [6], antibacterial [7–9], antifungal [10], antiviral [11], antitubercular and antimalarial [12], antidiabetic [13], anxiolytic [14] and anti-neurodegenerative [15] activities (Fig. 1).

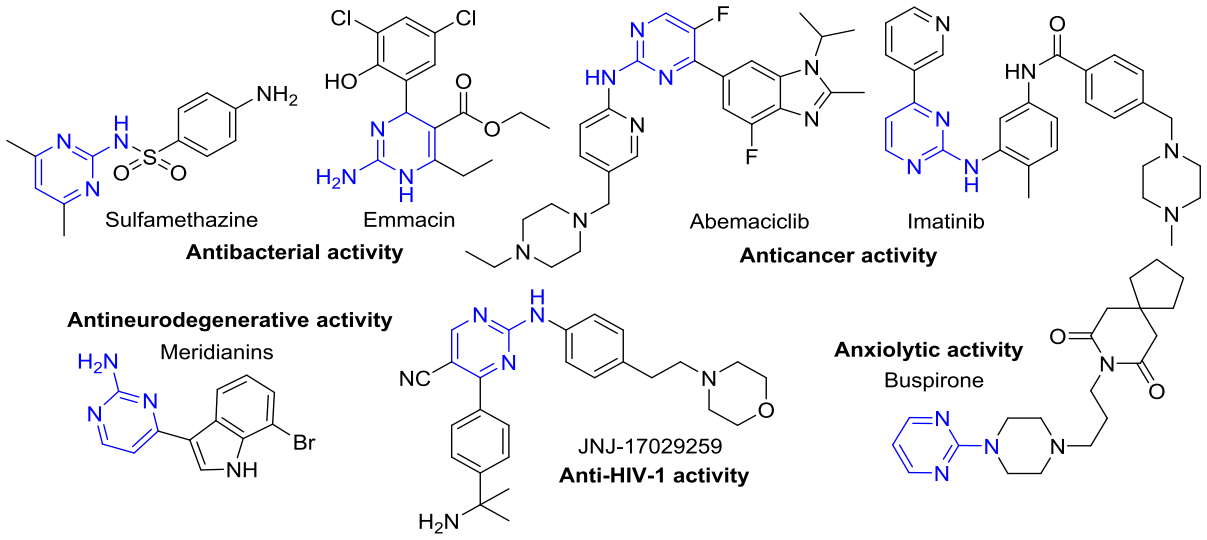


Figure 1. 2-Aminopyrimidine derivatives and their biological activity

Two primary methods are commonly used in the synthesis of substituted pyrimidines [16]. The first approach involves the condensation of fragments containing the desired substituents to construct the heterocyclic ring. The second approach involves introducing an amino group into the pyrimidine ring by substitution at position 2. However, the latter approach is less efficient and often results in low yields of the desired products, particularly in reactions with aryl amines where a large excess of the nucleophile is required. The pyrimidine ring can be synthesized via various condensation reactions involving different fragments in the overall process (Fig. 2).

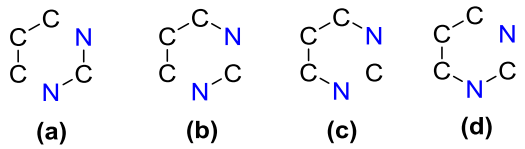


Figure 2. Variants of the condensation of the reagents to form the pyrimidine ring

Based on the literature data presented above, it is obvious to conclude that the 2-aminopyrimidine fragment is the most significant part responsible for the biological activity of its derivatives. This statement remains valid not only for substituted 2-aminopyrimidines but also for derivatives with condensed rings, including pteridines, pyridopyrimidines, imidazopyrimidines, purines, etc.

Experimental

Materials

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400 (400 and 100 MHz, respectively), Bruker AVANCE 500 (500 and 125 MHz, respectively) and Magritek spinsolve 80 carbon ultra (81 and 20 MHz, respectively) instruments. Residual solvent signals of DMSO-d_6 and $CDCl_3$ (2.49 and 39.9 ppm for ^{1}H and ^{13}C nuclei in DMSO-d_6; 7.25 and 77.0 ppm for ^{1}H and ^{13}C nuclei in $CDCl_3$) were used as the internal standards.

Chromato-mass spectrometric studies were carried out on a Trace GC Ultra chromatograph equipped with a DSQ II mass-selective detector in the electron ionization mode (70 eV) on a Thermo TR-5 MS quartz capillary column, 15 m long, 0.25 mm inner diameter, with a film thickness of the stationary phase of 0.25 μm. The splitless input mode was used. The carrier gas discharge was 20 ml/min. The carrier gas (helium) flow rate was 1 ml/min. Evaporator temperature 200 °C, transition chamber temperature 200 °C, ion source temperature 200 °C. The temperature of the column thermostat was changed according to the program: from 15 (5 min delay) to 220 °C at a rate of 20 °C per minute, to 290° at a rate of 15° per minute. The total analysis time was 30 min. The volume of the injected sample was 1 μl. The chromatograms were recorded in TIC mode. The range of mass scanning was 30–450 amu.

The progress of the reaction and the purity of the products were monitored by TLC on Sorbfil plates and visualized using iodine vapor or UV light.

The physicochemical and spectral characteristics of compounds **1a-c** were in agreement with literature data [22, 23].

Synthesis and Spectral Analysis of Synthesized Compounds

Ethyl 5-methyl-3-thioxo-2,3,4,5-tetrahydro-1*H*-1,5-methanonaphtho[1,2-*g*][1,3,5]oxadiazocine-13-carboxylate (1a) [23]. A mixture of 2-hydroxy-1-naphthaldehyde 1.72 g (10 mmol), thiourea 0.76 g (10 mmol) and acetoacetic ester 2.55 mL (20 mmol) in 15 mL of 2-propanol with 0.3 mL of trifluoroacetic acid catalyst was heated under MW irradiation for 5 seconds at 1 minute intervals. The total reaction time was 10 minutes. The precipitated solid was washed with water and 0.1 M NaOH solution. The solution was then decanted and the oil obtained was triturated with ice. The residue was purified by recrystallization from 2-propanol and chloroform. Yield: 1.300 g (38 %), white crystals, mp 290–291 °C.

^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.27 (t, 3H, *J* = 7.1, $OCH_2\underline{CH_3}$); 1.86 (s, 3H, CH_3); 3.38 (br.s, 1H, H-13); 4.17-4.23 (m, 2H, OCH_2); 5.19 (dd, 1H, *J* = 5.5, 2.8, H-1); 7.08 (d, 1H, *J* = 8.7, H-7); 7.42 (t, 1H, *J* = 7.1, H-10), 7.58 (t, 1H, *J* = 7.1, H-11); 7.83 (d, 1H, *J* = 9.2, H-8); 7.87 (d, 1H, *J* = 7.8, H-9); 8.15 (d, 1H, *J* = 8.7, H-12); 9.13 (s, 1H, NH-4); 9.49 (d, 1H, *J* = 4.6, NH-2).

^{13}C NMR spectrum (100 MHz, DMSO), δ, ppm: 14.0 (CH_2CH_3); 23.1 (CH_3); 42.5 (C-1); 44.3(C-13); 60.8 (OCH_2); 81.4 (C-5); 115.2 (C-12b); 118.0 (C-7); 121.9 (C-12); 123.9 (C-10); 127.1 (C-11); 128.3 (C-9); 128.6 (C-8a); 130.1 (C-8); 130.6 (C-12a); 148.2 (C-6a); 167.9 (C=O); 176.5 (C=S).

Ethyl 2-methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methanobenzo[g][1,3,5]oxadiazocine-11-carboxylate (1b) [22]. A mixture of 2-hydroxybenzaldehyde 1.04 mL (10 mmol), thiourea 0.76 g (10 mmol) and acetoacetic ester 2.55 mL (20 mmol) in 15 mL of 2-propanol with 0.3 mL of trifluoroacetic acid catalyst was refluxed at 60–70 °C for 12 hours. The precipitated yellow solid was washed with water and 0.1 M NaOH solution. The residue was purified by recrystallization from 2-propanol. Yield: 1.081 g (37 %), white crystals, mp 218–220 °C.

^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.22 (t, 3H, *J*=7.1 Hz, $OCH_2\underline{CH_3}$); 1.77 (s, 3H, 2-CH_3); 4.14 (dk, 2H, *J* = 7.1, 3.2 Hz, $O\underline{CH_2}CH_3$); 4.58 (dd, 1H, *J* = 5.0, 2.7 Hz, 6-CH); 6.82 (d, 1H, *J* = 8.2 Hz, H-10); 6.93 (td, 1H, *J* = 7.6, *J* = 0.9, H-9); 7.17-7.23 (m, 2H, H-7,8); 9.12 (br. s, 2H, 2NH).

1-(2-Methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methanobenzo[g][1,3,5]oxadiazocin-11-yl)ethan-1-one (1c) [22]. A mixture of 2-hydroxybenzaldehyde 1.04 mL (10 mmol), thiourea 0.76 g (10 mmol) and acetylacetone 2.05 mL (20 mmol) in 15 mL of 2-propanol with 0.3 mL of trifluoroacetic acid catalyst was refluxed at 60–70°C for 12 hours. The precipitated dark pink solid was washed with water and 0.1 M NaOH solution. The residue was purified by recrystallization from 2-propanol. Yield: 1.336 g (51 %), white crystals, mp 228–229 °C.

^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.68 (s, 3H, 2-CH_3); 2.27 (s, 3H, $COCH_3$); 3.42 (br. s, 1H, 11-CH); 4.74 (dd, 1H, *J* = 5.2, *J* = 2.4, 6-CH); 6.82 (d, 1H, *J* = 8.0, H-10); 6.93 (td, 1H, *J* = 7.4, *J* = 1.0, H-9); 7.19–7.23 (m, 2H, H-7,8); 8.99 (d, 1H, *J* = 4.9, 5-NH); 9.04 (s, 1H, 3-NH).

Ethyl 4-(ethylthio)-2-methyl-5,6-dihydro-2*H*-2,6-methanonaphtho[2,3-g][1,3,5]oxadiazocine-13-carboxylate (3a). A mixture of 0.342 g (1 mmol) of **1a** with 0.276 g (2 mmol) of potassium carbonate in 3 mL of DMF was stirred at room temperature for 16 hours and 0.112 mL (1.5 mmol) of ethyl bromide was added dropwise. The mixture was then poured into water (100–200 ml) and a saturated aqueous salt solution (NaCl) was added. The residue was filtered, dried and recrystallized from 2-propanol. Yield: 0.333 g (90 %), white crystals, mp 139–142 °C.

^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ ppm: 1.08 (t, 3H, *J* = 7.3 Hz, $SCH_2\underline{CH_3}$); 1.32 (t, 3H, *J* = 7.0 Hz, $OCH_2\underline{CH_3}$); 1.90 (s, 3H, CH_3); 2.78–2.91 (m, 2H, SCH_2); 3.04 (br.s, 1H, H-13); 4.16-4.30 (m, 2H, OCH_2); 5.44 (s, 1H, NH); 5.63 (d, 1H, *J* = 2.4 Hz, H-1); 7.03 (d, 1H, *J* = 9.2 Hz, H-7); 7.36 (t, 1H, *J* = 7.6 Hz, H-10); 7.54 (t, 1H, *J* = 7.6 Hz, H-11); 7.66 (d, 1H, *J* = 9.2 Hz, H-8); 7.75 (d, 1H, *J* = 7.9 Hz, H-9); 8.28 (1H, d, *J* = 8.5 Hz, H-12).

^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ ppm: 14.1, 14.4, 23.8, 25.2, 43.6, 50.9, 61.0, 81.3, 117.1, 118.1, 122.8, 123.7, 126.8, 128.0, 129.1, 129.2, 131.9, 147.9, 155.9, 169.2.

Ethyl 4-(ethylthio)-2-methyl-5,6-dihydro-2*H*-2,6-methanobenzo[g][1,3,5]oxadiazocine-11-carboxylate (3b) obtained by analogy to **3a** from 0.292 g (1 mmol) of **1b**, 0.276 g (2 mmol) potassium carbonate and 0.112 mL (1.5 mmol) of ethyl bromide in DMF. Yield: 0.272 g (90 %), light grey crystals, mp 156–159 °C.

^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ ppm: 1.09 (t, 3H, *J* = 7.3 Hz, $SCH_2\underline{CH_3}$); 1.30 (t, 3H, *J* = 7.0 Hz, $OCH_2\underline{CH_3}$); 1.91 (s, 3H, CH_3); 2.71–2.87 (m, 2H, SCH_2); 3.05 (s, 1H, H-11); 4.10-4.24 (m, 2H, OCH_2); 5.52 (s, 1H, NH); 5.59 (d, 1H, *J* = 2.4 Hz, H-1); 6.74 (1H, d, *J* = 7.8 Hz, H-10); 6.88 (t, 1H, *J* = 7.2 Hz, H-9); 7.10 (t, 1H, *J* = 7.1 Hz, H-8); 7.21 (d, 1H, *J* = 6.9 Hz, H-7).

1-(4-(Ethylthio)-2-methyl-5,6-dihydro-2*H*-2,6-methanobenzo[g][1,3,5]oxadiazocin-11-yl)ethan-1-one (3c) obtained by analogy to **3a** from 0.262 g (1 mmol) of **1c**, 0.276 g (2 mmol) potassium carbonate and 0.112 mL (1.5 mmol) of ethyl bromide in DMF. Yield: 0.261 g (90 %), white crystals, mp 166–169 °C.

^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ ppm: 1.03 (t, 3H, *J* = 7.0 Hz, $SCH_2\underline{CH_3}$); 1.63 (s, 3H, CH_3); 2.19 (s, 3H, $COCH_3$); 2.67-2.74 (m, 2H, SCH_2); 3.24 (s, 1H, H-11); 5.04 (d, 1H, *J* = 1.2 Hz, H-6); 6.77 (d, 1H, *J* = 7.9 Hz, H-10); 6.85 (t, 1H, *J* = 7.3 Hz, H-9); 7.12 (t, 1H, *J* = 7.0 Hz, H-8); 7.23 (d, 1H, *J* = 6.7 Hz, H-7); 8.14 (s, 1H, NH).

^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ ppm: 14.8 ($CH_2\underline{C}H_3$), 22.6 (SCH_2), 23.5 (CH_3), 28.8 ($CO\underline{C}H_3$), 49.2 (C-11), 52.6 (C-6), 81.7 (C-2), 116.3 (C-10), 120.2 (C-8), 125.5 (C-6a), 128.4 (C-9), 129.3 (C-7), 150.9 (C-10a), 154.7 (C-4), 204.2 (C=O).

Ethyl 4-(2-ethoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-pyrimidinecarboxylate (4). A mixture of 0.292 g (1 mmol) of **1b** with 0.276 g (2 mmol) of potassium carbonate in 3 mL of DMF was stirred at room temperature and after 2 hours 0.112 mL (1.5 mmol) of ethyl bromide was added dropwise. Then the mixture was poured into water (100–200 ml) and a saturated aqueous salt solution (NaCl) was added. The residue was filtered, dried and recrystallized from 2-propanol. Yield: 0.224 g (70 %), light yellow powder, mp 147–150 °C.

^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ ppm: 1.08 (t, 3H, *J* = 7.0 Hz, $OCH_2\underline{CH_3}$); 1.46 (t, 3H, *J* = 7.0 Hz, $OCH_2\underline{CH_3}$); 2.40 (s 3H, CH_3); 4.01-4.17 (m, 4H, 2 $O\underline{CH_2}CH_3$); 5.73 (d, 1H, *J* = 2.4 Hz, H-6); 6.84–6.87 (m, 2H, H-3',4' Ar); 7.01 (dd, 1H, *J* = 7.6, 1.5 Hz, H-6' Ar); 7.23 (td, 1H, *J* = 7.6, 1.8 Hz, H-5' Ar); 7.29 (br. s, 1H, 3-NH); 8.10 (br.s, 1H, 1-NH). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ ppm: 14.0, 14.9, 18.2, 51.3, 60.2, 63.6, 100.0, 111.5, 120.4, 127.2, 128.5, 129.5, 144.2, 156.2, 165.4, 174.5. MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 320.03 (100), 291.03 (59), 275.07 (16), 247.02 (63), 244.97 (78), 198.99 (39), 170.99 (31), 152.89 (13).

Ethyl 4-methyl-2-morpholinopyrimidine-5-carboxylate (5a) [17]. Method A. A mixture of 0.370 g (1 mmol) **3a** with 0.870 g (10 mmol) of morpholine was heated for 8 hours. The solvent was then evaporated under vacuum and the residue was triturated with water. The precipitate was filtered, dried and recrystallized from 2-propanol. Yield: 0.045 g (18%), grey powder, mp 87–93 °C.

Method B. A mixture of 0.320 g (1 mmol) **3b** with 0.870 g (10 mmol) of morpholine was heated at 150 °C for 8 hours. The solvent was then evaporated under vacuum and the residue was triturated with water. The precipitate was filtered, dried and recrystallized from 2-propanol. Yield: 0.045 g (18 %), grey crystals, mp 90–93 °C.

^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ ppm: 1.37 (t, 3H, *J* = 7.3 Hz, $OCH_2\underline{CH_3}$); 2.65 (s, 3H, CH_3); 3.76 (br.t, 4H, *J* = 4.6 Hz, $N(CH_2)_2$); 3.92 (br. t, 4H, *J* = 4.9 Hz, $O(CH_2)_2$); 4.32 (q, 2H, *J* = 6.9 Hz, OCH_2); 8.82 (s, 1H, H-6). ^{13}C NMR spectrum (101 MHz, $CDCl_3$) δ ppm 14.3 ($OCH_2\underline{CH_3}$), 25.0 (CH_3), 44.1 ($N(CH_2)_2$), 60.4 (OCH_2), 66.8 ($O(CH_2)_2$), 111.9, 160.8 (C-6), 161.1, 165.5, 170.2 (C=O). MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 221.12 (76), 206.04 (34), 190.10 (100), 176.07 (37), 164.09 (44), 148.06 (40), 136.08 (46), 93.07 (13).

1-(4-Methyl-2-morpholinopyrimidin-5-yl)ethan-1-one (5c) obtained by analogy to **5a** from 0.290 g (1 mmol) of **3c** with 0.870 g (10 mmol) of morpholine. Yield: 0.033 g (15 %), yellowish brown oil.

MS (EI) *m/z* (I_{rel}, %): $[M]^+$ 251.10 (69), 236.05 (17), 220.06 (100), 206.04 (59), 194.06 (44), 177.97 (17), 166.05 (56), 148.01 (10), 138.00 (16), 93.04 (9).

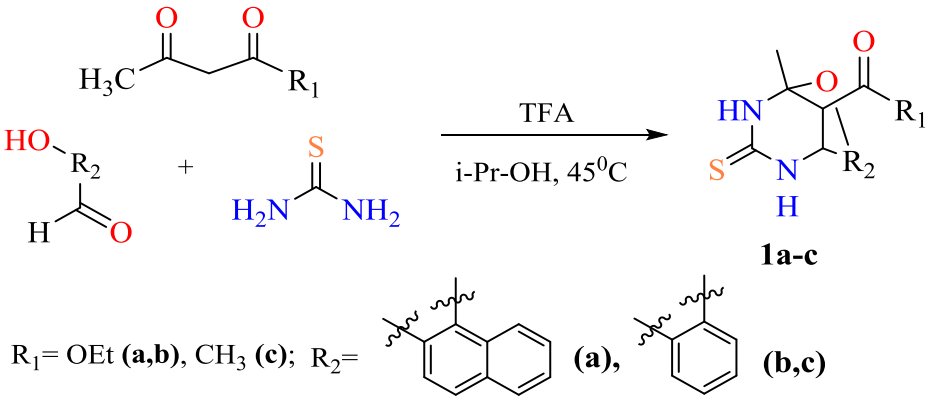
Results and Discussion

It is well known that salicylaldehyde and other derivatives of 2-hydroxybenzaldehyde behave differently from simple aromatic aldehydes in many reactions due to the presence of two reactive centres, the electrophilic carbonyl carbon atom and the nucleophilic hydroxy group. The synthesis of 3-acetylcoumarin is just one example of how this attribute is frequently used in the creation of various heterocyclic compounds [18, 19].

The articles [20–23] revealed that when salicylaldehyde, urea (or thiourea) and specific dicarbonyl compounds were subjected to the Biginelli reaction in the presence of trifluoroacetic (or hydrochloric) acid

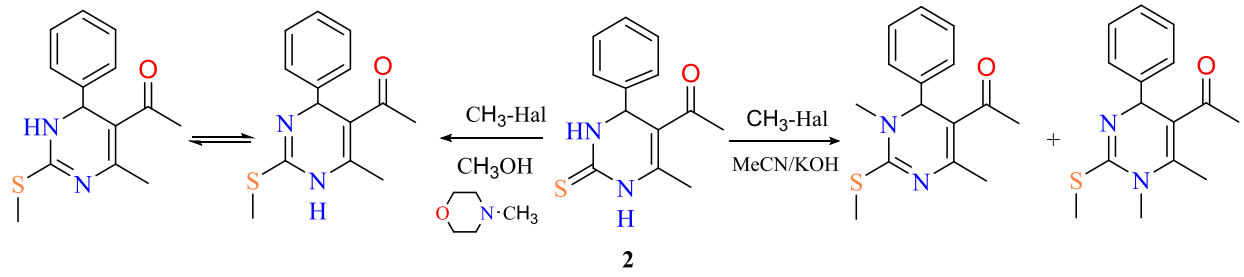
catalysts, the expected cyclization products of 4-aryl-3,4-dihydropyrimidin-2-ones (or 2-thiones) were not formed. Instead, the reaction resulted in the formation of derivatives of 3,4,5,6-tetrahydro-2H-2,6-methano[1,3,5]-benzo[g]oxadiazocines, chemical and biological properties of which were minimally studied. Therefore, this group of compounds is of great practical interest as they have the potential to be valuable candidates for extensive biological screening and can serve as starting materials for the synthesis of various biologically active molecules.

The starting materials for the Biginelli reaction, 2,6-methanobenzo- and 1,5-methanonaphtho-[1,3,5]oxadiazocines, were synthesized according to the Scheme 1:



Scheme 1. Formation of 2,6- methanobenzo- and 1,5- methanonaphtho[1,3,5]oxadiazocine derivatives using One-pot Biginelli Reaction

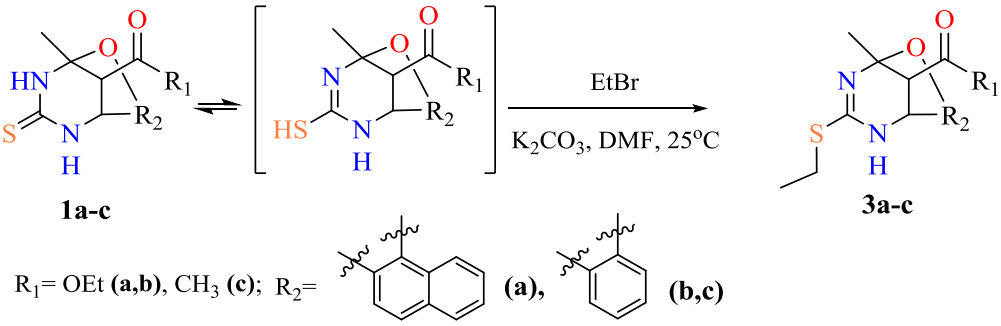
The literature provides only a limited number of examples on alkylation reactions involving structural analogues of benzoxodiazocines — pyrimidinethiones. It has been reported [24] that alkylation of 3,4-dihydropyrimidine-2-thione-5-carboxylic acid derivatives in methanol leads to the formation of 2-alkylthio derivatives and subsequent alkylation yields in 2,3-dialkyl derivatives as the primary products. The authors [25] investigated the alkylation of 3,4-dihydropyrimidine(1H)-2-thione **2** not only under standard conditions (methanol in the presence of N-methylmorpholine), but also in the system of acetonitrile — concentrated solution of KOH, which is also used for the alkylation of 3,4-dihydropyrimidine(1H)-2-thiones [26] (Scheme 2).



Scheme 2. Alkylation reaction of **2** in methanol with N-methylmorpholine

Upon treatment of alkyl halides in methanol with N-methylmorpholine, it undergoes S-alkylation reaction, while in the system of acetonitrile and aqueous KOH solution, a mixture of S(2), N(1)- and S(2), N(3)-alkylation products is formed. The composition of the tautomeric mixture of S-monoalkyl derivatives has been characterized, along with the regioselectivity of the dialkylation reaction.

Since the derivatives of diazocines **1a-c** contain a cyclic thiourea fragment capable of thion-thiol tautomerism, the alkylation reaction was carried out with ethyl bromide in DMF in the presence of potassium carbonate. As expected, due to the stronger nucleophilic properties of the thiol group compared to the nitrogen atom, S-alkylation products of compounds **1a-c** were obtained, as shown in Scheme 2, yielding in compounds **3a-c**.

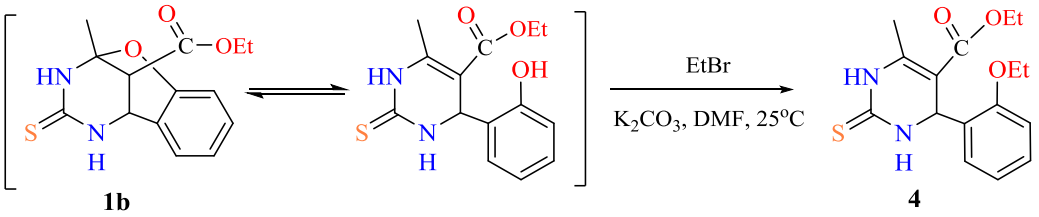


Scheme 3. Alkylation reaction of 2,6- methanobenzo- and 1,5- methanonaphtho[1,3,5]oxadiazocine derivatives

The structure of the alkylated derivatives **3a-c** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The presence of S-ethyl-2,6-methanobenzoxadiazocines **3c** was confirmed by the detection of specific spectroscopic signals, including a doublet of quartets of the methylene protons at 2.67-2.74 ppm, a triplet of methyl protons at 1.03 ppm originating from the S-ethyl group, and a singlet corresponding to the NH proton at 8.14 ppm. It is noteworthy that in the spectrum of the reaction mixture of compound **3c**, signals corresponding to the protons of the N-ethyl group were observed at 3.7–3.8 ppm. However, these signals exhibited significantly lower intensity compared to the S-isomer, indicating a lower degree of alkylation at the nitrogen atom. The approximate ratio of the alkylation products was estimated based on the signal intensities as 9:1 in favor of the S-ethyl derivative over the N-ethyl derivative.

Remarkable results were obtained in the alkylation of ethyl 2-methyl-4-thioxo-3,4,5,6-tetrahydro-2H-2,6-methanobenzo[g][1,3,5]oxadiazocine-11-carboxylate **1b** with ethyl bromide when it was added 2 hours after the dissolution of the starting compound **1b** in DMF. Upon treatment of the reaction mixture, a white crystalline compound was isolated from the predominant oily mass in a yield of about 10 %. This compound was easily purified by recrystallization. Analysis of the ^{1}H NMR spectrum revealed several important observations. Firstly, the methylene protons of both the S- and N-ethyl isomers, which were present in compound **3c** at 2.7 and 3.7 ppm respectively, were not observed. Secondly, the broad singlet corresponding to the H-11 proton in the original compound **1b** was not detected. Thirdly, the methyl group protons, previously observed as a singlet at 1.77 ppm in compound **1b**, experienced a significant shift to a weaker region at 2.40 ppm. Similarly, the H-6 proton transformed from a doublet of doublets at 4.48 ppm (due to interactions with the methylene and N-H protons) in compound **1b** to a clear doublet at 5.73 ppm. In addition, a quartet system in the range of 4.01–4.13 ppm, characteristic of the OSN2 groups, i.e., the methylene protons of the ethoxy moiety, was observed. Examination of the spectral data obtained indicated that the alkylation process in DMF resulted in the conversion of benzoxadiazocine **1b** to its structural isomer, the 3,4-dihydropyrimidine analogue **4**. This compound was subsequently alkylated with ethyl bromide to yield the corresponding ethyl 4-(2-ethoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxo-5-pyrimidinecarboxylate **4**.

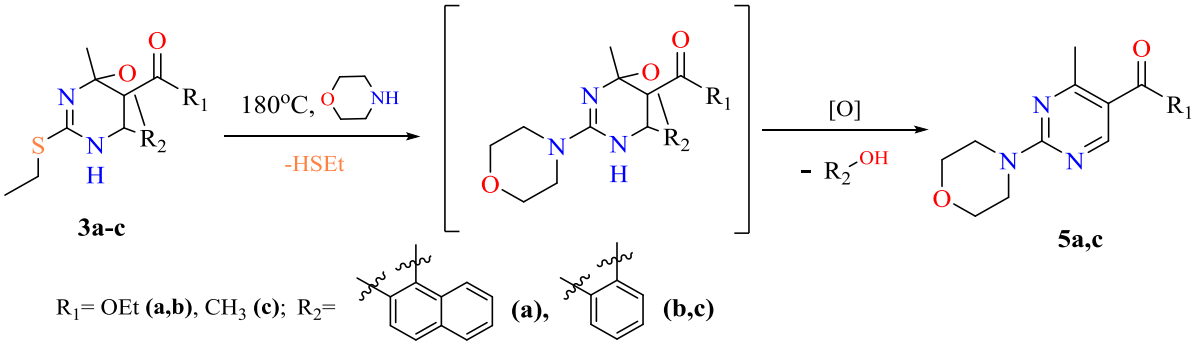
The above conclusions regarding the proposed structure of compound **4** were fully supported by the analysis of the ^{13}C NMR spectrum. Previous studies cited in reference [27] have demonstrated comparable structural isomerizations of benzo[g]oxadiazocines in solutions of DMF or DMSO. These isomerizations were based on ^{1}H NMR spectra recorded in DMSO-d_6, which showed the structural transformation of the initial nitrobenzo[g]oxadiazocines into their respective hydroxyphenyl 3,4-dihydropyrimidinethiones.



Scheme 4. Structural isomerization of benzoxadiazocine **1b** into 3,4-dihydropyrimidine analogue **4**

From the data obtained it can be concluded that even slight variations in the conditions of alkylation reaction for oxadiazocines, due to its potential thione-thiol tautomerism in the basic medium (DMF + K_2CO_3) and the opening of the oxazine ring, can lead to the formation of various products, including S-, N-, and O-alkylation.

In order to obtain 2-amino substituted benzo[g]oxadiazocine derivatives, the structural analogs of 2-aminopyrimidines, nucleophilic substitution reactions with S-ethyl-1,5-methanonaphthoxadiazocine **3a** and S-ethyl-1,3-benzoxadiazocines **3b** and **3c** in the excess of morpholine were carried out.



Scheme 5. Formation of 2-aminopyrimidine derivatives using amination reaction with morpholine

NMR spectroscopic analysis of the reaction products indicated that, in addition to nucleophilic substitution by morpholine, elimination of the corresponding naphthol or phenol occurred. This elimination was followed by aromatization of the pyrimidine ring, ultimately leading to the formation of 2-morpholinyl-substituted pyrimidines **5a** and **5c**. The observed low reaction yields could be attributed to the partial tarring of the reaction mixture during the nucleophilic substitution reaction performed at an elevated temperature of 150 °C. It is worth noting that only a limited number of examples and rather complex, multi-step methods for obtaining similar 2-amino-substituted pyrimidines are reported in the literature [28, 29].

Conclusions

Thus, the study conducted using methanobenzo[g][1,3,5]oxadiazocine and methanonaphtho[2,3-g]-[1,3,5]oxadiazocine as model compounds has demonstrated their ability to undergo alkylation with ethyl bromide under relatively mild reaction conditions, resulting in the formation of S-ethyl derivatives. However, even minor modifications in the alkylation reaction conditions of oxadiazocines, such as the timing of ethyl bromide addition, the potential for thione-thiol tautomerism in the basic medium and the opening of the oxazine ring, lead to the formation of diverse products, including S-, N-, and O-alkylation.

These S-ethyl derivatives of oxadiazocines exhibit enhanced lipophilicity of the oxadiazocine core and possess good cell permeability, making them highly suitable for bioscreening applications. In addition, under the influence of a secondary amine — morpholine, the obtained S-ethyl derivatives of oxadiazocines undergo nucleophilic substitution of the ethylthiol group. During the substitution process, phenol (or naphthol) is eliminated and the dihydropyrimidine core undergoes oxidative aromatization. As a result, 2-amino-substituted pyrimidines are formed. This methodology offers a valuable approach to synthesizing a range of functional derivatives of 2-aminopyrimidines, which are typically challenging to access.

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Conflicts of Interest

The authors declare no conflict of interest.

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