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SYNTHESIS, STRUCTURE, AND ANTIRADICAL ACTIVITY OF NEW METHANO[1,3]THIAZOLO[2,3-*d*][1,3,5]BENZOXA-DIAZOCINE DERIVATIVES

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The reaction of 2,6-methano[1,3,5]benzoxadiazocines, obtained in Biginelli reaction, with chloroacetic acid derivatives produced previously unknown tricyclic methano[1,3]thiazolo[2,3-d][1,3,5]benzoxadiazocines, the structure of which was proved by ^{1}H NMR spectroscopy and X-ray structural analysis. The methano[1,3]thiazolo[2,3-d][1,3,5]benzoxadiazocines showed no antiradical activity in contrast to the starting 2,6-methano[1,3,5]benzoxadiazocines.

Keywords: 2*H*-2,6-methano[1,3,5]benzoxadiazocines, salicylic aldehyde, thiourea, Biginelli reaction, intramolecular heterocyclization, X-ray structural analysis.

There has been a recent significant increase in the number of publications devoted to the chemistry of 3,4-dihydropyrimidin-2-ones(thiones) **1**, **2**, obtained by three-component condensation in Biginelli reaction. The reasons for this include not only the preparative accessibility of 3,4-dihydropyrimidin-2-ones(thiones) **1**, **2**, but also the broad spectrum of pharmacological activity characteristic of these compounds, including analgesic, antibacterial, antihypertensive, and other properties [1-3], which motivate the further study of such compounds.

The mechanism of Biginelli reaction is now well understood [4], many derivatives of 3,4-dihydropyrimidin-2-ones **1** and 3,4-dihydropyrimidine-2-thiones **2** with various functional substituents have been synthesized, many preparative methods have been developed and patented, including solvent-free microwave-assisted procedures, and highly effective catalysts have been discovered, leading to significant increase of yields and shorter reaction times [5-13].

The range of applications for 3,4-dihydropyrimidine-2-thiones was also extended when 4-(3-hydroxyphenyl)pyrimidine-2-thione derivative **3** was synthesized, which is known as monastrol, a compound characterized by a completely new mechanism of anticancer activity through specific influence on cell division (mitosis) [14]. It is not surprising that synthesis of new derivatives of monastrol **3** has been recently performed by the research groups of Bose [15] and Dondoni [16].

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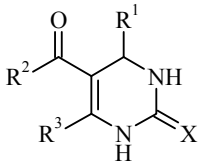
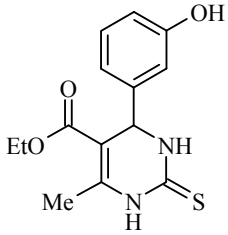
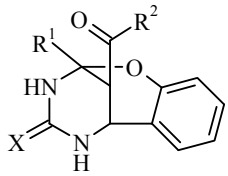


1 (X = O)
2 (X = S)



3
(monastrol)



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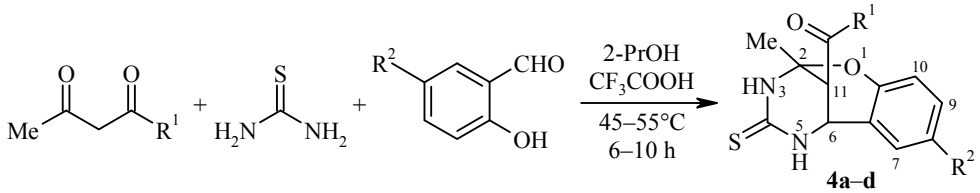
Nevertheless, despite more than century of studying Biginelli reaction, new and interesting facts are still being discovered. Thus, when 3-hydroxybenzaldehyde, acetoacetic ester, and thiourea are used in the classical Biginelli reaction, the major product is monastrol **3**. Derivatives of 2-hydroxybenzaldehyde are known to behave in many reactions differently than simple aromatic aldehydes due to the adjacent positions of hydroxyl and aldehyde groups, and this is often used in various types of heterocyclization [17]. In particular, doubts about the direction of Biginelli reaction with 2-hydroxybenzaldehyde were expressed in a review article [13]. The authors of another publication [18] established 20 years ago that the condensation of salicylic aldehyde, urea (or thiourea), and some derivatives of acetoacetic ester in the presence of catalytic amounts of hydrochloric acid did not produce the standard cyclization products, 4-aryl-3,4-dihydropyrimidin-2-ones(thiones) **1**, **2**, but rather the derivatives of 2-methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methano[1,3,5]-benzoxadiazocine **4**, the chemical and biological properties of which have not yet been investigated. Similar compounds were later obtained by using other dicarbonyl compounds or aliphatic alicyclic ketones [19].

However, a recent report [20] showed that, depending on the reaction conditions, at various temperature regimes and in the presence of trichloroacetic acid as catalyst, products may be obtained from Biginelli reactions in two possible directions, either the the standard cyclization products 3,4-dihydropyrimidin-2-ones(thiones) **1**, **2** (when refluxing in ethanol for 2-4 h), or benzoxadiazocine **4** (when heating in ethanol at 40°C for 7-9 h). We should note that the formation of 3,4-dihydropyrimidin-2-ones(thiones) based on 2-hydroxybenzaldehyde has not been described before. At the same time, literature sources [18, 20] propose various and contradictory mechanisms for the formation of methano[1,3,5]benzoxadiazocines **4**, which do not allow to unequivocally conclude about kinetic or thermodynamic control over the formation of the aforementioned cyclization products. For example, in the work [21] similarly to [18] (over 6-8 hours of refluxing in methanol), and in contrast to method [20], a solvent-free reaction under microwave irradiation produced only methano[1,3,5]benzoxadiazocines **4**.

We studied the possible cyclization of 2-hydroxybenzaldehyde or 5-bromo-2-hydroxybenzaldehyde with thiourea and acetoacetic ester or acetylacetone into the corresponding heterocyclic derivatives **4a-d** (Table 1). Heating in DMF at 110-130°C in the presence of acetic acid allowed to obtain compounds **4a-d** in approximately 30% yields; refluxing in ethanol in the presence of $MnCl_2$ catalyst gave the target products in higher yields and better purity. At the same time, the standard cyclization products, 3,4-dihydropyrimidine-2-thiones were not isolated, in contrast to previously reported data [20]. The best yields and purity of target products were obtained by performing the cyclization in 2-propanol at 45-55°C in the presence of trifluoroacetic acid.



4a–d

a R^1 = OEt, R^2 = H; **b** R^1 = Me, R^2 = H; **c** R^1 = OEt, R^2 = Br; **d** R^1 = Me, R^2 = Br

TABLE 1. Physicochemical Characteristics of Compounds **4a-d**, **5a-d**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield*, %
		C	H	N		
4a	$C_{14}H_{16}N_2O_3S$	57.09 / 57.52	5.82 / 5.52	9.74 / 9.58	228-229	47
4b	$C_{13}H_{14}N_2O_2S$	60.01 / 59.52	5.02 / 5.38	10.84 / 10.68	218-220	59
4c	$C_{14}H_{15}BrN_2O_3S$	45.57 / 45.29	4.32 / 4.07	7.16 / 7.55	225-226	43
4d	$C_{13}H_{13}BrN_2O_2S$	45.95 / 45.76	3.48 / 3.84	8.54 / 8.21	221-222	49
5a	$C_{16}H_{16}N_2O_4S$	57.51 / 57.82	4.57 / 4.85	8.14 / 8.43	150-152	92
5b	$C_{15}H_{14}N_2O_3S$	59.90 / 59.59	4.89 / 4.67	9.08 / 9.27	179-180	95
5c	$C_{16}H_{15}BrN_2O_4S$	46.36 / 46.73	3.31 / 3.68	6.69 / 6.81	182-184	91
5d	$C_{15}H_{13}BrN_2O_3S$	47.63 / 47.26	3.17 / 3.44	7.19 / 7.35	180-182	85

*Product yield without recrystallization. In the case of compounds **5a-d**, yields are indicated for reaction with chloroacetamide.

The structure of heterocyclic derivatives **4a-d** was unequivocally confirmed by IR and ^{1}H NMR spectroscopy, mass spectrometry (Table 2), as well as X-ray structural analysis (Fig. 1), which showed the presence of only single (2*S*,6*S*,11*R*)-enantiomer in the monocrystal. We should note that the 6-CH proton in the ^{1}H NMR spectra of compounds **4a-d** appeared as a double doublet (interaction with 11-CH and 5-NH protons), while the signal of 11-CH proton was a doublet (compounds **4a**,**c**) or unsplit singlet (compounds **4b**,**d**). The possibility of ethoxycarbonyl group rotation around C(11)–COOEt bond was manifested in ^{1}H NMR spectra of compounds **4a**,**c** by the presence of duplicated signals of OCH_2 protons.

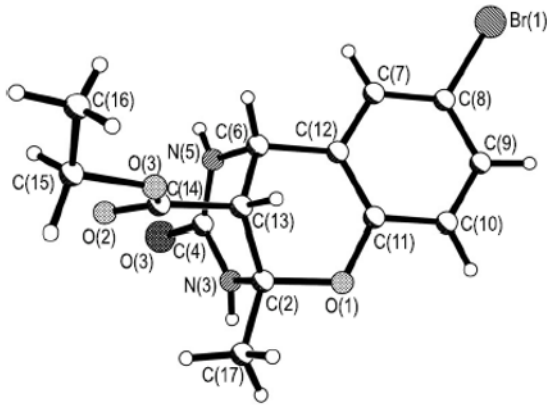


Fig. 1. The molecular structure of ester **4c**.

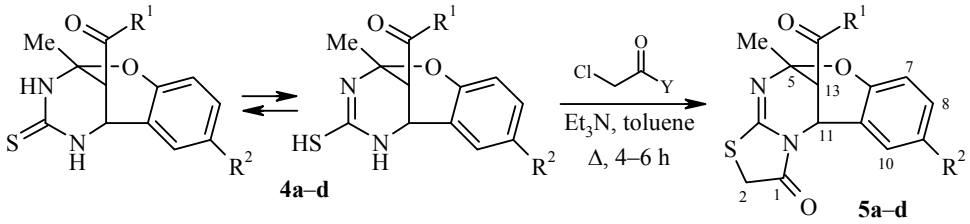
We interpreted the complications in performing this reaction as due to several parallel reactions – a possible three-component Biginelli condensation of the starting reagents into the ethyl ester of 4-(5-bromo-2-hydroxyphenyl)-6-methyl-2-thioxo-3,4-dihydropyrimidine-5-carboxylic acid, as well as the associated condensation reaction of 2-hydroxybenzaldehyde and acetoacetic ester. Thus, reaction of 5-bromo-2-hydroxybenzaldehyde with thiourea and acetoacetic ester in DMF allowed to isolate 3-acetyl-6-bromo-2*H*-chromen-2-one in approximately 5% yield.

TABLE 2. Spectral Characteristics of Compounds **4a-d**, **5a-d**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)	Mass spectrum, *m/z* (I_{rel}, %)
4a	3364, 3167, 3085, 1728, 1564, 1491	1.22 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.77 (3H, s, 2-CH_3); 3.30 (1H, d, *J* = 2.8, 11-CH); 4.14 (2H, dq, *J* = 3.2, *J* = 7.1, $OC\underline{H}_2CH_3$); 4.58 (1H, dd, *J* = 5.0, *J* = 2.7, 6-CH); 6.82 (1H, d, *J* = 8.2, H-10); 6.93 (1H, td, *J* = 7.6, *J* = 0.9, H-9); 7.17-7.23 (2H, m, H-7,8); 9.12 (2H, br. s, 2NH)	—
4b	3228, 3148, 2957, 1715, 1566, 1513	1.68 (3H, s, 2-CH_3); 2.27 (3H, s, $COCH_3$); 3.42 (1H, br. s, 11-CH); 4.74 (1H, dd, *J* = 5.2, *J* = 2.4, 6-CH); 6.82 (1H, d, *J* = 8.0, H-10); 6.93 (1H, td, *J* = 7.4, *J* = 1.0, H-9); 7.19-7.23 (2H, m, H-7,8); 8.99 (1H, d, *J* = 4.9, 5-NH); 9.04 (1H, s, 3-NH)	—
4c	3370, 3273, 3172, 1721, 1613, 1468	1.23 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.78 (3H, s, 2-CH_3); 3.36 (1H, d, *J* = 2.7, 11-CH); 4.16 (2H, dq, *J* = 1.6, *J* = 7.1, $OC\underline{H}_2CH_3$); 4.63 (1H, dd, *J* = 5.0, *J* = 2.6, 6-CH); 6.82 (1H, d, *J* = 8.5, H-10); 7.35-7.40 (2H, m, H-7,9); 9.09 (1H, d, *J* = 4.7, 5-NH); 9.18 (1H, s, 3-NH)	372 [M (^{81}Br)]$^+$ (27), 370 [M (^{79}Br)]$^+$ (27), 325 (21), 200 (17), 199 (100), 198 (16), 171 (37), 89 (28), 84 (18), 42 (75)
4d	3388, 3216, 2940, 1714, 1535, 1485	1.68 (3H, s, 2-CH_3); 2.27 (3H, s, $COCH_3$); 3.44 (1H, br. s, 11-CH); 4.80 (1H, dd, *J* = 5.1, *J* = 2.4, 6-CH); 6.82 (1H, d, *J* = 8.5, H-10); 7.36-7.40 (2H, m, H-7,9); 8.97 (1H, d, *J* = 4.3, 5-NH); 9.16 (1H, s, 3-NH)	342 [M (^{81}Br)]$^+$ (4), 340 [M (^{79}Br)]$^+$ (4), 325 (2), 323 (2), 63 (11), 43 (100), 42 (40), 39 (10)
5a	3000, 1720, 1605, 1484, 1371	1.18 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 1.71 (3H, s, 5-CH_3); 3.43 (1H, d, *J* = 2.3, 13-CH); 4.08 (2H, br. s, 2-CH_2); 4.14 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 5.58 (1H, d, *J* = 2.0, 11-CH); 6.87 (1H, d, *J* = 8.3, H-7); 6.92 (1H, td, *J* = 7.5, *J* = 1.1, H-9); 7.22-7.28 (2H, m, H-8,10)	—
5b	2990, 1711, 1618, 1486, 1367	1.63 (3H, s, 5-CH_3); 2.29 (3H, s, $COCH_3$); 3.66 (1H, d, *J* = 2.1, 13-CH); 3.96 (1H, d, *J* = 17.4) and 4.02 (1H, d, *J* = 17.4, 2-CH_2); 5.58 (1H, d, *J* = 2.0, 11-CH); 6.84 (1H, d, *J* = 8.1, H-7); 6.90 (1H, td, *J* = 7.4, *J* = 0.9, H-9); 7.20-7.27 (2H, m, H-8,10)	—
5c	2970, 1726, 1610, 1474, 1367	1.18 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 1.70 (3H, s, 5-CH_3); 3.45 (1H, d, *J* = 2.2, 13-CH); 4.11 (1H, d, *J* = 17.4) and 4.15 (1H, d, *J* = 17.4, 2-CH_2); 4.14 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 5.62 (1H, d, *J* = 2.2, 11-CH); 6.87 (1H, d, *J* = 8.7, H-7); 7.34 (1H, d, *J* = 2.5, H-10); 7.43 (1H, dd, *J* = 8.7, *J* = 2.5, H-8)	412 [M (^{81}Br)]$^+$ (5), 410 [M (^{79}Br)]$^+$ (5), 239 (13), 211 (17), 115 (27), 89 (38), 72 (65), 67 (31), 63 (54), 46 (100), 45 (78), 43 (42), 42 (96), 39 (33)
5d	2960, 1721, 1620, 1478, 1369	1.65 (3H, s, 5-CH_3); 2.31 (3H, s, $COCH_3$); 3.67 (1H, d, *J* = 2.1, 13-CH); 3.95 (1H, d, *J* = 17.5) and 4.01 (1H, d, *J* = 17.5, 2-CH_2); 5.60 (1H, d, *J* = 2.0, 11-CH); 6.87 (1H, d, *J* = 8.5, H-7); 7.35 (1H, d, *J* = 2.3, H-10); 7.43 (1H, dd, *J* = 8.5, *J* = 2.3, H-8)	—

3,4-Dihydropyrimidine-2-thiones **2** attract the attention of many chemistry researchers by the presence of several reactive nucleophilic centers, enabling various reactions of mono- and dialkylation and acylation [22, 23].

We previously demonstrated a convenient method for the cyclization of 4-aryl-3,4-dihydropyrimidine-2-thiones into 3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidines [24] and explored some details of intramolecular cyclization [25]. While continuing these investigations, we attempted to perform analogous heterocyclization with derivatives of [1,3,5]benzoxadiazocine **4a-d**. Compounds **4a-d** were found to cyclize quite readily upon refluxing in toluene or benzene with slight excess of methyl or ethyl chloroacetate in the presence of triethylamine, forming previously unreported tricyclic methano[1,3]thiazolo[2,3-*d*][1,3,5]benzoxadiazocines **5a-d**.



4a–d **5a–d**

a R^1 = OEt, R^2 = H; **b** R^1 = Me, R^2 = H; **c** R^1 = OEt, R^2 = Br; **d** R^1 = Me, R^2 = Br; Y = OMe, OEt, NH_2

It was also shown that using α-chloroacetamide in this reaction instead of methyl chloroacetate led to not only higher yields and better purity of target products, but also easier isolation of products from the reaction mixture. The formation of methano[1,3]thiazolo[2,3-*d*][1,3,5]benzoxadiazocine derivatives **5a-d** was proved by the absence of NH and thio group absorption bands in the IR spectra, and the lack of the NH proton signals in ^{1}H NMR spectra. The methylene protons of thiazole ring in compounds **5b-d** were non-equivalent and manifested as two doublets with spin-spin coupling constants of 17.4-17.5 Hz. The ^{1}H NMR spectra for the products from reactions of compound **4a-d** with chloroacetic amide or esters did not contain additional ester or amide group signals, pointing to the fact that reaction did not stop at alkylation stage, but rather led to intramolecular cyclization with thiazole ring formation.

Of particular interest was the structural study of products from the reactions of [1,3,5]benzoxadiazocines **4a-d** with chloroacetic acid derivatives and the differences of these compounds from the previously described thiazolopyrimidines [24], because the participation of 3-NH or 5-NH protons in the thione-thiol tautomerism may lead to the formation of methano[1,3]thiazolo[3,2-*c*][1,3,5]benzoxadiazocine or methano-[1,3]thiazolo[2,3-*d*][1,3,5]benzoxadiazocine, respectively. With this goal we performed an X-ray structural study of compound **5c**, the structure of which is presented in Figure 2.

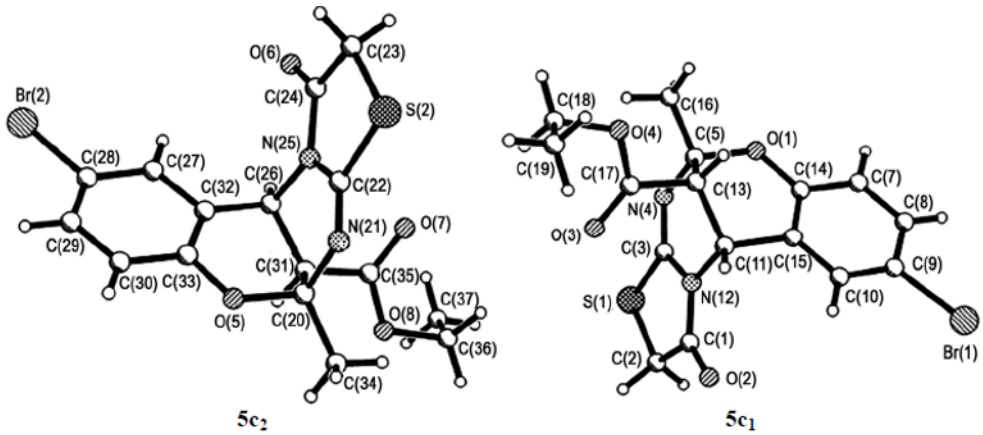


Fig. 2. Spatial structure of ester **5c** (two independent molecules are shown without taking the mutual orientation into account).

The crystal structure of compound **5c**, similarly to the previously studied 5-(2,4-dimethoxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid [24], contained two geometrically independent molecules **5c$_1$** and **5c$_2$** (two enantiomers (5*R*,11*R*,13*S*) and (5*S*,11*S*,13*R*), respectively) packed in one independent unit cell. The bond lengths and valence angles in the structure were close to standard values [26]. The structure **5c$_1$** consisted of a central eight-membered oxadiazocine ring O(1)C(5)N(4)C(3)N(12)C(11)C(15)C(14), connected by methane bridge with the ester group, and thus forming two fused rings – pyrimidine N(4)C(3)N(12)C(11)C(13)C(5) and pyran O(1)C(5)C(13)C(11)C(15)C(14) – with the C(13) atom in common. The oxadiazocine ring was fused from one side with the benzene ring and from the other side with the thiazolidine ring.

Similarly to our previously obtained related structure [24], the thiazolidine ring in each molecule was nearly planar with sulfur atom deviating from the plane of other atoms by 0.09 Å, while the O(2) and O(6) atoms of carbonyl groups were in that plane. The pyrimidine ring assumed a nearly ideal "sofa" conformation (ΔC_s^{13} = 1.14 Å and ΔC_s^{31} = 4.37 Å) with the bridging C(13) and C(31) atoms in molecules **5c$_1$** and **5c$_2$** deviating by 0.70 and 0.74 Å, respectively. This ring could also assume a "twist-boat" conformation as in the structure of 5-nitro-4-(2-nitrophenyl)-6-phenyl-3,4-dihydro-1*H*-pyrimidin-2-one [27]. The pyran rings in molecules **5c$_1$** and **5c$_2$** also assumed a "sofa" conformation. The bromine atom in both molecules had equatorial orientation and was located in phenyl ring plane (torsion angles C(7)–C(8)–C(9)–Br(1) -178.95°, C(30)–C(29)–C(28)–Br(2) 177.61°).

While continuing the search for new types of compounds with antioxidant activity [28], some of the obtained compounds were tested for antiradical effect towards the radical cation 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{+\cdot}$). The quench rates of $ABTS^{+\cdot}$ were compared for the studied compounds against a standard, semisynthetic water-soluble analog of vitamin E, (±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (commercial name Trolox). The use of Trolox enabled the expression of antiradical activity through Trolox Equivalent Antioxidant Capacity (TEAC), where TEAC values indicate the concentration of Trolox in mmol/l (mM) that quenches $ABTS^{+\cdot}$ with effectiveness equivalent to 1 mM of the analyzed compound.

We established as a result of our study that the starting compounds **4a-c** exhibited antiradical activity against $ABTS^{+\cdot}$ with TEAC values 0.62±0.04 (62% of Trolox activity), 0.75±0.03 (75% of Trolox activity), and 1.27±0.11 (activity 1.27 times exceeding that of Trolox), respectively. Compounds **5a-c** did not exhibit antiradical activity under the test conditions.

Thus, derivatives of 2-methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methano[1,3,5]benzoxadiazocine were used to obtain previously unknown tricyclic derivatives of 5-methyl-1-oxo-1,2,5,11-tetrahydro-5,11-methano[1,3]thiazolo[2,3-*d*][1,3,5]benzoxadiazocine, the structure of which was proved by ^{1}H NMR spectroscopy and X-ray structural analysis. The synthesized methano[1,3]thiazolo[2,3-*d*][1,3,5]benzoxadiazocines were demonstrated to have no antiradical activity, in contrast to the starting 2,6-methano-[1,3,5]benzoxadiazocines, probably due to the lack of active NH protons in their molecules.

EXPERIMENTAL

IR spectra were recorded on an Infralum FT-801 spectrometer. ^{1}H NMR spectra were acquired on Bruker DRX-400 (400 MHz, compounds **4**, **5 a**,**b**) and Bruker DRX-500 (500 MHz, compounds **4**, **5 c**,**d**) instruments in DMSO-d_6, with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT Incos 50 instrument with direct introduction of sample (EI ionization, 70 eV). Elemental analysis was performed on a Carlo Erba 1106 CHN instrument. Melting points were determined on a Boetius apparatus. The reaction progress and the purity of the obtained compounds were controlled by TLC on Sorbfil plates, visualization with iodine vapor or under UV light.

Synthesis of Ethyl 2-Methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methano[1,3,5]benzoxadiazocine-11-carboxylate (4a), 1-(2-Methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methano[1,3,5]benzoxadiazocin-

11-yl)ethanone (4b), and their 8-Bromo Derivatives 4c,d (General Method). Method A. A mixture of acetoacetic ester or acetylacetone (24 mmol), finely ground thiourea (1.5 g, 20 mmol), 2-hydroxybenzaldehyde or 5-bromo-2-hydroxybenzaldehyde (20 mmol), and CF_3COOH (0.3 ml) in 2-PrOH (30 ml) was stirred at 45-55°C until complete dissolution of thiourea (1-2 h), followed by stirring at room temperature for additional 6-10 h. The reaction mixture with precipitated product was then cooled, the precipitate was filteted off, washed with cold 2-PrOH, and dried. Evaporation of filtrate yielded additional 10-20% crop of product. The obtained compounds were recrystallized several times from 2-PrOH or EtOH until constant melting temperature was achieved.

Ethyl 8-Bromo-2-methyl-4-thioxo-3,4,5,6-tetrahydro-2*H*-2,6-methano[1,3,5]benzoxadiazocine-11-carboxylate (4c). Method B. A mixture of acetoacetic ester (2.60 g, 20 mmol), thiourea (1.60 g, 21 mmol), 5-bromo-2-hydroxybenzaldehyde (4.02 g, 20 mmol), and 3-5 drops of AcOH in DMF (5 ml) was heated for 3 h at 110-130°C in a flask with reflux condenser, then treated with EtOH (5 ml) and refluxed for additional 3 h. The precipitated crystals of 3-acetyl-6-bromo-2*H*-chromen-2-one were filteted off and washed with EtOH. The filtrate was diluted with ice water (100 ml). Water layer was decanted from the dark-red oil that separated, the oil was washed with water several times and recrystallized several times from 1:1 mixture of 2-PrOH–hexane. Yield 35%, colorless transparent crystals.

Method C. A mixture of acetoacetic ester (2.60 g, 20 mmol), thiourea (1.60 g, 21 mmol), 5-bromo-2-hydroxybenzaldehyde (4.02 g, 20 mmol), and $MnCl_2 \cdot 2H_2O$ (3.20 g, 20 mmol) in EtOH (15 ml) was heated in a flask with reflux condenser for 6 h. The solution was poured into a mixture of ice water (300 ml) and ice (100 g). The light-yellow precipitate that formed was filteted off and recrystallized from a 1:1 mixture of 2-PrOH–hexane. Yield 40%.

Synthesis of Ethyl 5-Methyl-1-oxo-1,2,5,11-tetrahydro-5,11-methano[1,3]thiazolo[2,3-*d*][1,3,5]benzoxadiazocine-13-carboxylate (5a), 13-Acetyl-5-methyl-5,11-dihydro-5,11-methano[1,3]thiazolo[2,3-*d*]-[1,3,5]benzoxadiazocin-1(2*H*)-one (5b), and their 9-Bromo Derivatives 5c,d (General Method). A mixture of methano[1,3,5]benzoxadiazocine **4a-d** (2.0 mmol), methyl chloroacetate or chloroacetamide (2.2 mmol), and Et_3N (0.4 g, 4.0 mmol) in anhydrous toluene (10 ml) or benzene in the case of reaction with chloroacetamide was refluxed for 4-6 h in a flask with reflux condenser. The precipitated crystals of $Et_3N \cdot HCl$ were filteted off, and washed with small amount of benzene, which was then combined with the filtrate and evaporated. The residue was triturated with hexane to fine powder. Several recrystallization steps, first from a 1:1 mixture of 2-PrOH–hexane, then from pure 2-PrOH yielded light-yellow crystals.

X-Ray Structural Investigation of Compound 4c. Crystals of compound **4c** ($C_{14}H_{15}BrN_2O_3S$, *M* 371.26) were grown over 3 days from EtOH. A colorless prismatic crystal (0.25×0.40×0.60 mm) was selected for the study. X-ray structural study was performed at room temperature on an Xcalibur Oxford Diffraction diffractometer with CCD-detector (CuKα radiation, λ 1.5418 Å, Enhance (Cu) X-ray Source fine focus X-ray tube, graphite monochromator). Crystals were monoclinic; *a* 17.104(2), *b* 8.660(12), *c* 20.544(3) Å; α 90.0, β 94.206(1), γ 90.0°; *V* 3034.8(2) $Å^3$; *Z* 8; *C*2/*c* space group. The experimental data were collected by using the CrysAlisPro software [29]. The integrated intensities were measured by ω-scanning method, with monochromatization by reflection from a graphite crystal. After averaging the equivalent reflections and removal of weak reflections with $I < 2\sigma(I)$, working array of 2640 reflections was obtained. Correction for absorption was performed by multiscan method with the CrysAlisPro software suite [29]. The structure was solved by direct method using the SHELXS-97 software suite [30] and refined by full matrix least squares method with the SHELXL-97 software [31]. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated from stereochemical criteria and refined by using the "rider" model. The probability factor after final refinement of positional and anisotropic thermal parameters R_1 0.0384. The molecular graphics were created by the XP program in the SHELXTL-Plus software suite [32]. Complete X-ray structural data set for compound **4c** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1024097).

X-ray Sructural Investigation of Compound 5c. The unit cell parameters and intensities of 6672 independent reflections for compound **5c** ($C_{16}H_{15}BrN_2O_4S$, *M* 411.28) were determined on an Xcalibur Oxford Diffraction diffractometer with CCD-detector (CuKα radiation, λ 1.5418 Å, Enhance (Cu) X-ray Source fine focus X-ray tube, graphite monochromator, θ/2θ-scanning, 2θ < 38°) at 20°C. Crystals were monoclinic; *a* 9.6212(3), *b* 21.1372(4), *c* 8.40730(10) Å; α 90.0, β 102.992(2), γ 90.0°; *V* 1665.99(6) Å^3; d_{calc} 1.456 g/cm^3; *Z* 4; $P2_1$ space group. Calculations were performed with 4497 reflections of intensity $I > 2\sigma(I)$. The structure was solved directly with the SIR-2002 software [33] and refined by full matrix least squares analysis in anisotropic approximation for non-hydrogen atoms. Hydrogen atom positions were calculated geometrically and refined by using the "rider" model. The final probability factors were R_1 0.0451, wR_2 0.1179. Geometry was refined with the SHELXL-97 software [31]. The complete X-ray structural data set for compound **5c** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 773784).

Biological Studies. The antiradical activity of compounds **4a-c**, **5a-c** was studied with regard to the radical cation 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^{+\cdot}$), using Antioxidant Assay Kit from Sigma-Aldrich according to the user manual supplied by manufacturer. The method was based on the principle of ferrylmyoglobin radical formation from metmyoglobin and hydrogen peroxide, which oxidizes ABTS with the formation of a radical cation $ABTS^{+\cdot}$. Adding various antiradical agents to the solution results in their interaction with $ABTS^{+\cdot}$ and rapid consumption ("quenching") of the latter. The consumption of $ABTS^{+\cdot}$ is accompanied by characteristic spectral changes, allowing to record the reaction rate [34].

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