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Synthesis of New Thiazolo[3,2-*b*][1,2,4]triazole Derivatives and Preliminary Evaluation of Their Biological Activity

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Heterocyclization of 3-[(1*H*-1,2,4-triazol-3-yl)thio]pentane-2,4-dione afforded 1-(6-methylthiazolo[3,2-*b*][1,2,4]-triazol-5-yl)ethan-1-one, the reactions of which with hydroxylamine, hydrazincarboxamide, hydrazincarbothioamide, hydrazine hydrate and *para*-toluenesulfonyl hydrazide resulted in the formation of the corresponding derivatives. 1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethan-1-one oxime reacted with alkyl halides and phenyl isocyanate to produce the corresponding *O*-alkyl- and *O*-phenylcarbamoyl derivatives. The growth regulating activity of the compounds obtained was studied.

Keywords: thiazolo[3,2-*b*][1,2,4]triazoles, 1-(6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethan-1-one oxime, heterocyclization, growth regulating activity

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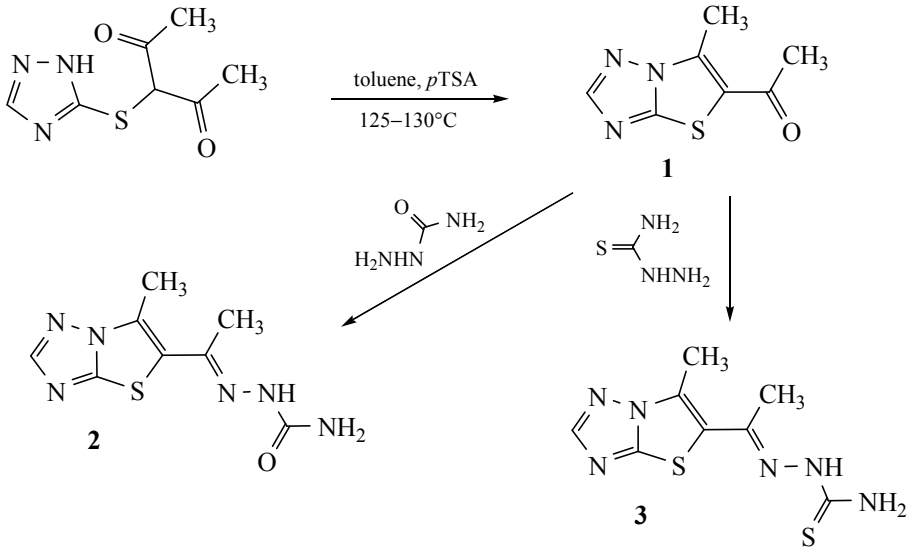
Derivatives of such nitrogen- and sulfur-containing five-membered heterocycles, as 1,3-thiazole and 1,2,4-triazole, have a broad spectrum of biological activity. A large number of drugs contain 2-aminothiazole and aminothiazole-2-thione fragments in their structure [1]. In recent years, much attention has been paid to the synthesis of fused systems based on thiazole and 1,2,4-triazole. Thus, bicyclic thiazolotriazoles have been synthesized by the reaction of 5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione with compounds containing a cyanomethylene group [2]. 2,6-Diarylthiazolo[3,2-*b*]-[1,2,4]triazoles with a similar structure were obtained by reacting 3-aryl-1*H*-1,2,4-triazole-5-thiols with 2,2-dibromo-1-arylethan-1-one [3]. Synthesis of 6-arylthiazolo[3,2-*b*][1,2,4]triazoles by the reaction of 1,2,4-triazole-5(1*H*)-thiol with 2-bromo-1-arylethan-1-ones has been reported in [4]. One of the compounds obtained, namely 6-(4-propoxyphenyl)thiazolo[3,2-*b*]-[1,2,4]triazole, showed a higher activity than carbamazepine. Polyheterocyclic compounds with anti-inflammatory and antiviral activity have been obtained on the basis of 1,2,4-triazole thioethers [5]. Some of the obtained derivatives based on 2-substituted 1-(6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethan-1-one showed antiviral and anti-mycobacterial activities [6, 7]. The original one-step method for the synthesis of 5,6-disubstituted thiazolo[3,2-*b*][1,2,4]triazoles based on the reaction of unsaturated ketones with bis(1*H*-1,2,4-triazolyl)sulfoxide has been proposed in [8]. The reaction of 5-aryl-2,4-dihydro-1,2,4-triazol-3(3*H*)-thiones with 2-bromo-1-phenylethan-1-one followed by cyclization of the resulting 1-phenyl-2-[(3-aryl-1*H*-1,2,4-triazol-5-yl)thio]ethan-1-ones afforded 2-aryl-6-phenylthiazolo[3,2-*b*][1,2,4] triazoles [9]. A similar approach has been used to obtain naphthyridinyl-substituted thiazolotriazoles under the action of microwave irradiation [10].

Among the synthesized compounds, substances with antimicrobial [3], antibacterial [6, 9], anticonvulsant [4], antiviral [10] and anti-inflammatory [11] activity were found. Some compounds were found to be inhibitors of platelet aggregation [12] and were similar in action to some well-known COX-2 inhibitors [8].

Given the fact that 1,3-thiazole and 1,2,4-triazole are the basic heterocycles of a large number of pesticides and plant growth regulators, as well as great interest in their fused bicyclic derivatives, herein we reported effective methods for the synthesis of some derivatives of fused bicyclic thiazolotriazoles and data on preliminary evaluation of their biological activity in

Scheme 1.



terms of finding new chemical plant protection agents and plant growth regulators.

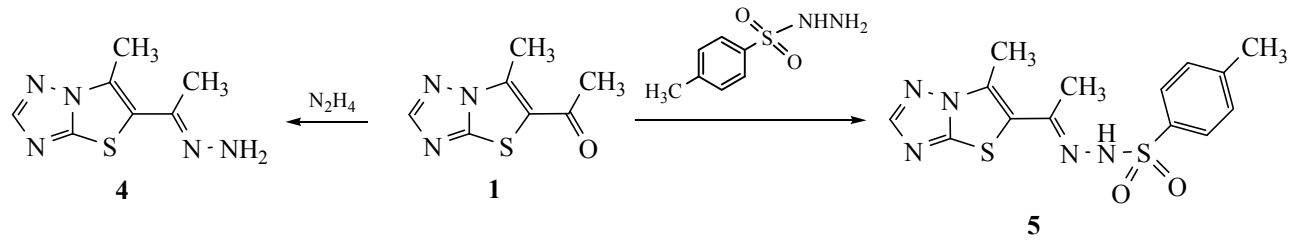
The starting 1-(6-methylthiazolo[3,2-*b*][1,2,4] triazol-5-yl)ethan-1-one **1** was synthesized by heterocyclization of the previously obtained 3-[(1*H*-1,2,4-triazol-3-yl)thio]pentane-2,4-dione [13] when heated at 125–130°C in toluene for 8–10 h in the presence of *para*-toluenesulfonic acid (*p*TSA). Further transformations of the obtained ketone **1** led to new fused bicyclic derivatives (Scheme 1). Thus, 2-{1-(6-methylthiazolo-[3,2-*b*][1,2,4]triazol-5-yl)ethylidene}hydrazine-1-carboxamide **2** and its corresponding thio-analogue **3** were synthesized by reacting compound **1** with hydrazinocarboxamide and hydrazinocarbothioamide, respectively.

The reaction of ketone **1** with hydrazine hydrate and *p*-toluenesulfonyl hydrazide led to the formation of 5-(1-hydrazonoethyl)-6-methylthiazolo[3,2-*b*][1,2,4]-triazole **4** and 4-methyl-*N*'-{1-(6-methylthiazolo[3,2-*b*]-[1,2,4]triazol-5-yl)ethylidene}benzenesulfonohydrazide **5**, respectively (Scheme 2).

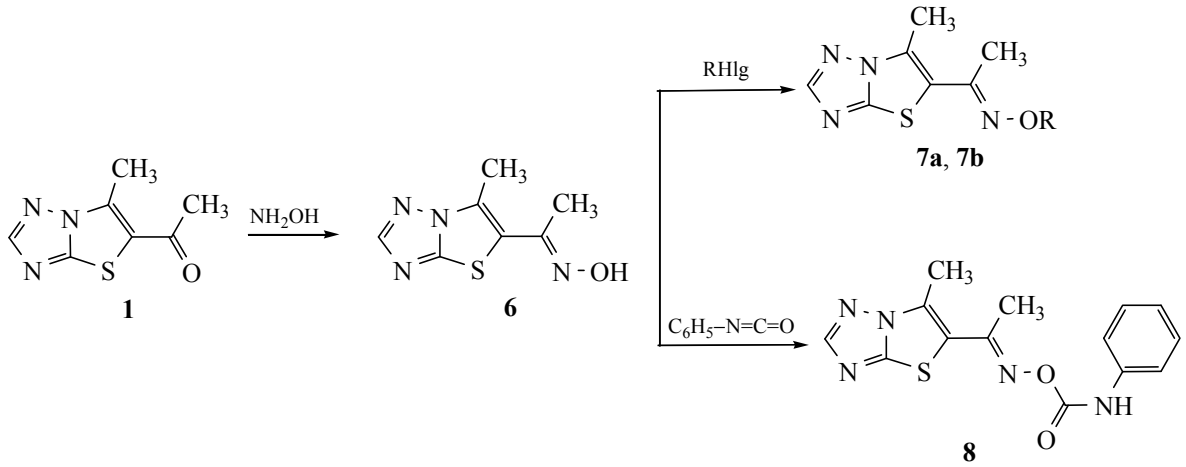
The reaction of compound **1** with hydroxylamine furnished 1-(6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethan-1-one oxime **6** (Scheme 3). Heating the latter with alkyl halides in DMF in the presence of KOH afforded alkyl substituted oximes **7a** and **7b**. The reaction of oxime **6** with phenyl isocyanate when heated in toluene in the presence of catalytic amounts of pyridine produced *O*-phenylcarbamoyloxime **8** (Scheme 3). For oxime **6** and its *O*-substituted derivatives **7** and **8**, *E*/Z isomerization at the C=N double bond is possible (Scheme 4). Indeed, in the ^{1}H and ^{13}C NMR spectra of these compounds, two sets of signals corresponding to the *E*- and *Z*-isomers are observed in a ratio of 1 : (3–4).

For the study of herbicidal, fungicidal and growth-regulating activities of the synthesized compounds, laboratory and vegetation studies were conducted. Oxime **6** and its derivatives **7a** and **7b** showed moderate herbicidal activity (60–70%) at 3 kg/ha. At the same time, almost all the studied compounds demonstrated a stimulating effect on plant growth. Experiments were performed on seeds and seedlings of *Phaseolus vulgaris L*. The effect of aqueous suspensions of compounds **1–8** and a solution of

Scheme 2.



Scheme 3.



R = C_3H_7 (**a**), $CH_2CH_2OC_6H_5$ (**b**).

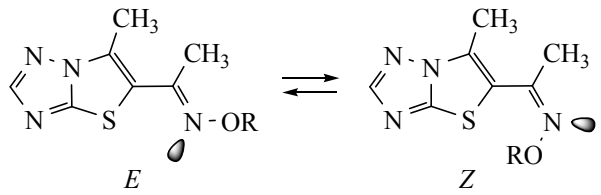
heteroauxin as a reference in concentrations of 25 and 50 mg/L on seed viability, their germination and seedling growth was studied. The activity of compounds varied in the range of 65–87% compared with heteroauxin (see the table). The substances that showed the greatest activity in the experiment (**1**, **5**, **6**, and **7a**) were chosen for detailed study and further field trials.

In conclusion, a simple and convenient method for the synthesis of 1-(6-methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethan-1-one was developed by heterocyclization of 3-{(1*H*-1,2,4-triazol-3-yl)thio}pentane-2,4-dione. As a result of its transformations, a number of derivatives were obtained, which, with preliminary biological screening, showed a stimulating effect on plant growth. The results of the study indicate the promise of finding new plant growth regulators in a series of fused bicyclic thiazolotriazole derivatives.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 NMR spectrometer (300 and 75 MHz, respectively) from DMSO-d_6 solutions. The reaction progress and individuality of the obtained compounds were monitored by TLC on Silufol UV-254 plates; eluting with acetone–hexane mixture (2 : 1). Melting points were determined by the capillary method.

Scheme 4.



Plant growth regulating activity of compounds **1**–**8**

Compound	*c*, mg/L	Plant growth regulating activity compared with heteroauxin, %
Heteroauxin	25	100
	50	100
1	25	81.2
	50	82.1
2	25	64.9
	50	65.7
3	25	63.3
	50	63.1
4	25	60.6
	50	66.5
5	25	84.8
	50	65.0
6	25	86.1
	50	87.0
7a	25	74.7
	50	–
7b	25	65.7
	50	66.1
8	25	69.1
	50	60.7

1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethan-1-one (1). A mixture of 3-{(1*H*-1,2,4-triazol-5-yl)thio}-pentane-2,4-dione (0.01 mol) in 10 mL of toluene and catalytic amount of *p*-toluenesulfonic acid was refluxed for 10 h. After removal of toluene, the residue was treated with water, filtered off and dried. Yield 78%, mp 138–140°C. ^{1}H NMR spectrum, δ, ppm: 2.61 s (3H, 6-CH_3), 2.91 s (3H, $COCH_3$), 8.18 s (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 12.56, 28.74, 126.60, 134.84, 154.57, 156.59, 189.39. Found, %: C 46.28; H 3.79; N 23.30; S 17.48. C $_7H_7N_3OS$. Calculated, %: C 46.40; H 3.89; N 23.19; S 17.69.

2-{1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)-ethylidene}hydrazine-1-carboxamide (2). A mixture of hydrazincarboxamide hydrochloride (0.01 mol) and compound **1** (0.01 mol) in water (15 mL) was stirred for 4 h at 100°C. The resulting precipitate was filtered off and dried. Yield 85%, mp 274–275°C. ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, 6-CH_3), 2.71 s (3H, N=C–CH_3), 7.62 br. s and 8.27 br. s (2H, NH_2), 9.09 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 12.23, 15.20, 126.48, 127.04, 139.07, 152.97, 155.42, 156.21. Found, %: C 40.19; H 4.15; N 35.45; S 13.60. $C_8H_{10}N_6OS$. Calculated, %: C 40.33; H 4.23; N 35.27; S 13.46.

2-{1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)-ethylidene}hydrazine-1-carbothioamide (3). Compound **1** (0.01 mol) was added to a mixture of hydrazincarbothioamide (0.01 mol) and a 36% aqueous HCl solution (0.01 mol). The mixture was stirred for 4–5 h at 100°C. The resulting precipitate was filtered off and dried. Yield 90%, mp 267–268°C. ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H, 6-CH_3), 2.73 s (3H, N=C–CH_3), 7.41 br. s and 8.32 br. s (2H, NH_2), 10.54 br. s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 12.49, 16.00, 125.87, 128.82, 142.95, 153.26, 155.70, 178.99. Found, %: C 37.66; H 3.77; N 33.27; S 25.03. $C_8H_{10}N_6S_2$. Calculated, %: C 37.78; H 3.96; N 33.04; S 25.21.

5-(1-Hydrazonoethyl)-6-methylthiazolo[3,2-*b*]-[1,2,4]triazole (4). A mixture of compound **1** (0.01 mol), hydrazine hydrochloride (0.01 mol) and water (10 mL) was stirred for 3-4 h at 80–90°C. The resulting precipitate was filtered off, washed with water and dried. Yield 88%, mp 270–272°C. ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, 6-CH_3), 2.88 br. s (2H, NH_2), 2.92 s (3H, N=C–CH_3), 8.18 s (1H, CH). Found, %: C 43.12; H 4.71; N 35.60; S 16.19. $C_7H_9N_5S$. Calculated, %: C 43.06; H 4.65; N 35.87; S 16.42.

4-Methyl-*N*'-[1-(6-methyl[1,3]thiazolo[3,2-*b*][1,2,4]-triazol-5-yl)ethylidene]benzenesulfonohydrazide (5). A mixture of compound **1** (0.01 mol) and *para*-toluenesulfonyl hydrazide (0.01 mol) in water (10 mL) was stirred for 1 h at 60–70°C. The resulting precipitate was filtered off, washed with water and dried. Yield 90%, mp 232–234°C. ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3-tolyl), 2.38 s (3H, 6-CH_3), 2.63 s (3H, N=C–CH_3), 7.39–7.74 m (4H, C_6H_4), 8.28 s (1H, CH), 10.78 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 12.24, 15.82, 20.77, 125.43, 127.49, 128.71, 129.28, 135.63, 143.39, 147.81, 153.23, 155.68. Found, %: C 48.03; H 4.27; N 20.22; S 18.12. $C_{14}H_{15}N_5O_2S_2$. Calculated, %: C 48.12; H 4.33; N 20.04; S 18.35.

1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)-ethan-1-one oxime (6). To a solution of NaOH (0.01 mol) in water (3 mL) at 0°C was added a solution of hydroxylamine hydrochloride (0.01 mol) in 5 mL of water, compound **1** (0.01 mol) and ethanol (5 mL). The mixture was kept at 20°C for 24 h, then heated for 2 h at 50–60°C. After cooling, the precipitate was filtered off and dried. Yield 91%, mp 178–180°C. ^{1}H NMR spectrum, δ, ppm (*Z*:*E* = 3:1): 2.29 (*Z*) s and 2.31 (*E*) s (3H, 6-CH_3), 2.65 (*E*) s and 2.71 (*Z*) s (3H, N=C–CH_3), 7.99 (*Z*) s and 8.01 (*E*) s (1H, CH), 11.50 (*Z*) s and 11.57 (*E*) s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 12.09 (*Z*), 12.86 (*Z*), 12.99 (*E*), 21.08 (*E*), 116.69 (*E*), 123.99 (*Z*), 126.16 (*Z*), 127.65 (*E*), 142.22 (*E*), 147.20 (*Z*), 152.89 (*E*), 154.76 (*Z*), 154.82 (*Z*), 155.04 (*E*)**.** Found, %: C 42.74; H 4.02; N 28.22; S 16.08. $C_7H_8N_4OS$. Calculated, %: C 42.85; H 4.11; N 28.55; S 16.34.

Synthesis of compounds 7a, 7b. A mixture of KOH (0.01 mol) and compound **6** (0.01 mol) in DMF (10 mL) was stirred for 2 h until salt formation completed, then 0.01 mol of propyl bromide or 2-phenoxyethyl bromide was added. The reaction mixture was kept for 24 h at room temperature, then heated for 2 h at 60–70°C until pH = 7 was adjusted. DMF was removed and residue was treated with water. Precipitate was filtered off and dried.

1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethan-1-one *O*-propyloxime (7a). Yield 85%, mp 48–50°C. ^{1}H NMR spectrum, δ, ppm (*Z*:*E* = 3:1): 0.98 (*Z*) t and 0.99 (*E*) t (3H, CH_3-propyl, *J* = 6.9 Hz), 1.73 m (2H, CH_2), 2.30 (*Z*) s and 2.33 (*E*) s (3H, 6-CH_3), 2.67 (*E*) s and 2.72 (*Z*) s (3H, N=C–CH_3), 4.09 (*E*) t and 4.12 (*Z*) t (2H, OCH_2, *J* = 6.7 Гц), 8.01 (*Z*) s and 8.04 (*E*) s (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 9.89 (*Z*), 10.09 (*E*), 12.22 (*Z*), 13.03 (*E*), 13.62 (*Z*), 21.10 (*E*), 21.64 (*E*), 21.78 (*Z*), 75.41 (*Z*), 75.58 (*E*), 116.24 (*E*), 122.46 (*Z*), 127.09 (*Z*), 128.52 (*E*), 143.23 (*E*), 147.85 (*Z*),

153.01, 154.96 (*Z*), 155.27 (*E*). Found, %: C 50.52; H 5.90; N 23.70; S 13.62. $C_{10}H_{14}N_4OS$. Calculated, %: C 50.40; H 5.92; N 23.51; S 13.46.

1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)-ethan-1-one *O*-(2-phenoxyethyl)oxime (7b). Yield 97%, mp 70–72°C. ^{1}H NMR spectrum, δ, ppm (*Z* : *E* = 3.5 : 1): 2.32 (*Z*) s and 2.33 (*E*) s (3H, 6-CH_3), 2.62 (*E*) s and 2.73 (*Z*) s (3H, N=C–CH_3), 4.26 m (2H, NO–CH_2), 4.48 m (2H, $C_6H_5OCH_2$), 6.85–7.26 m (5H, C_6H_5), 8.03 (*Z*) s and 8.04 (*E*) s (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 12.25 (*Z*), 12.97 (*E*), 13.91 (*Z*), 21.17 (*E*), 65.22 (*E*), 65.43 (*Z*), 71.98 (*E*), 72.42 (*Z*), 113.98 (*E*), 114.02 (*Z*), 116.05, 120.16 (*Z*), 122.05 (*E*), 127.58 (*E*), 128.76 (*Z*), 128.91, 144.36 (*E*), 149.12 (*Z*), 153.04, 155.04 (*Z*), 155.23 (*E*), 157.97 (*E*), 158.08 (*Z*). Found, %: C 56.81; H 5.02; N 17.51; S 10.33. $C_{15}H_{16}N_4O_2S$. Calculated, %: C 56.94; H 5.10; N 17.71; S 10.14.

1-(6-Methylthiazolo[3,2-*b*][1,2,4]triazol-5-yl)ethan-1-one *O*-(phenylcarbamoyl)oxime (8). A mixture of compound **6** (0.01 mol), phenyl isocyanate (0.01 mol), absolute toluene (15 mL) and catalytic amount of pyridine was refluxed for 2 h. Precipitate was filtered off and recrystallized from a 50% aqueous ethanol. Yield 88%, mp 202–204°C. ^{1}H NMR spectrum, δ, ppm (*Z* : *E* = 4 : 1): 2.52 (*Z*) s and 2.53 (*E*) s (3H, 6-CH_3), 2.63 (*E*) s and 2.83 (*Z*) s (3H, N=C–CH_3), 6.96–7.58 m (5H, C_6H_5), 8.10 (*Z*) s and 8.14 (*E*) s (1H, CH), 9.47 (*E*) s and 9.58 (*Z*) s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 12.67 (*Z*), 12.75 (*E*), 15.18, 115.41, 117.48, 118.50 (*Z*), 121.23, 122.41 (*Z*), 128.02 (*E*), 128.12 (*Z*), 129.98 (*E*), 138.06 (*Z*), 150.16 (*E*), 153.48 (*E*), 154.54 (*E*), 155.47 (*Z*)**.** Found, %: C 53.40; H 4.22; N 22.42; S 10.31. $C_{14}H_{13}N_5O_2S$. Calculated, %: C 53.32; H 4.16; N 22.21; S 10.17.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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