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Dedicated to the memory of Professor
Evgeny Mikhailovich Alov
on the occasion of his 75th anniversary

SYNTHESIS OF NEW HERBICIDES FROM THE CLASS OF SULFONYLUREAS

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Abstract. *The authors first synthesised sulfonylurea derivatives incorporating 6-methyluracil and 1,3,4-thiadiazole fragments with 79-81 % yield. The authors conducted field tests of the obtained compounds to determine their herbicidal activity. As a result, the synthesised compounds exhibit a herbicidal activity (53%) close to that of Rubit (61%) and higher than that of Magnum herbicide (41%).*

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Introduction

Among chemical plant protection products (CPCPs), herbicides have a leading role. Weeds cause multifaceted harm to agriculture. They successfully compete with cultivated plants for light, nutrients, and water. Some types of weedy vegetation are a breeding ground for pests. For example, cereal flies (Swedish, Hessian, winter, etc.), which cause significant damage to cereal crops. Moreover, they occur on various species of wheatgrass and other weeds, which provide them with shelter and a source of food. Weeds make it difficult to do field work: tillage, plant care, harvesting. Furthermore, the admixture of weed seeds reduces the quality of the crop [1].

The purpose of this work is to synthesise new effective herbicides from the class of sulfonylureas (Fig. 1).

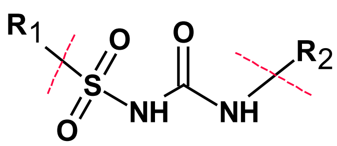


Fig. 1. General structural formula of sulfonylurea

In the 1970s of the 20th century, a new class of herbicides was obtained – sulfonylureas. They were previously known as anti-diabetic drugs.

Sulfonylurea derivatives demonstrate high herbicidal activity at rates 1-2 orders of magnitude lower compared to traditionally used herbicides [2]. They make up approximately 10% of the global herbicide market [3].

Their mechanism of action is very particular. They have an inhibitory effect on the enzyme acetolactate synthase (ALS). Indeed, the enzyme catalyses the biosynthesis of essential amino acids – leucine, isoleucine, and valine [4, 5]. Since there is no ALS in warm-blooded animals, drugs from the sulfonylurea class are safe for animals, fish, and birds [6].

Main body

The head of the Department of Organic Chemistry, Doctor of Chemical Sciences, Professor E.M. Alov was at the origin of synthesis of CPCPs at Yaroslavl State Technical University, Yaroslavl, Russia. He was the first to discover the growth-stimulating activity of sulfonylalkylcarboxylic acids on cuttings of tea-hybrid rose [7]. Several compounds belonging to this class have been patented this year as growth stimulators for plants. Nowadays, field tests are being conducted on more than 10 cereals and legumes [8].

By using computer screening in the synthesis planning stage, the most promising compounds can be identified, saving considerable time and resources. To assess the potential biological activity, cropCSM programme was used. It allows us to predict the probability of activity or inactivity of a compound based on its structural formula. The work of cropCSM is based on analysing the relationship between structure and activity of substances from a training sample of more than 4000 biologically active compounds [9].

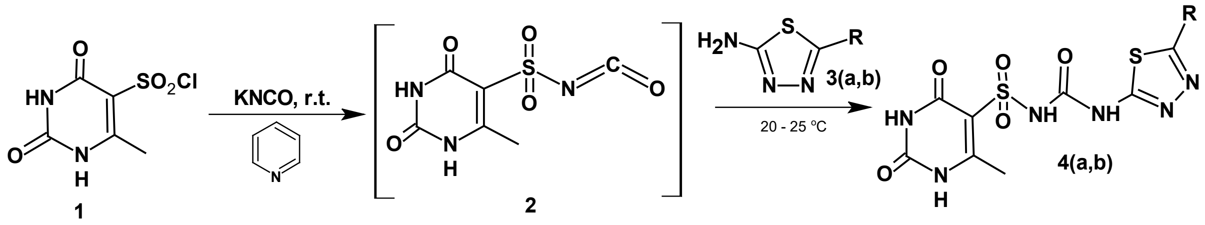
We input the formula of the compound under study into the programme. Then it was converted into the language programmed in cropCSM. The outputs presented predictions about herbicidal activity and toxicity. The cropCSM programme is available in an online version. A biological activity sample assay is provided as an illustration (Fig. 2).

Herbicidal Activity	Environmental Toxicity			Human Toxicity			
Herbicide Activity	Honey Bee Toxicity	Avian Toxicity	Minnow Toxicity	AMES Toxicity	Rat Acute Toxicity (LD50)	Rat Chronic Toxicity (LOAEL)	SMILES
Yes	No	No	2.269	No	1515.3	19.0	C1(C(=C(N(C(N1[H])=O)[H])C)[S](N([H])C(=O)N([H])C2=NN=C(S2)C(F)(F)F)(=O)=O)=O

Fig. 2. cropCSM: prediction of herbicide activity

In this work, sulfonylurea has 6-methyluracil as the substituent R1 and 1,3,4-thiadiazole as R2 (Figure 1). This choice of substituents is due to high herbicidal activity of the pyrimidine base, and 1,3,4-thiadiazole is used in the continuous-acting herbicides sulfodiazole, thiazafluron, and tebuterone. The combination of these fragments in the molecule allows us to expect high biological activity [10].

There are several methods for the preparation of such substituted sulfonylureas: a) based on carbamates; b) based on urea derivatives; c) using phosgene [11-13]. This study showed that the best method for the obtaining was the one in which we used 6-methyluracil-5-sulfochloride and potassium cyanate as starting compounds in the presence of pyridine using acetonitrile as solvent (Scheme 1). We then added amine as free base to the reaction mixture. After completion of the reaction, we treated the contents of the reactor with acetic acid and water. Then we isolated the target product (Scheme 1) [14]. Under these conditions, new sulfonylurea derivatives were synthesised in good yields of 79 - 81 %.



3, 4 a R = CH_3, **b** R = CF_3

Scheme 1

The structure of the synthesised compounds **4(a, b)** was confirmed by a combination of IR, NMR spectroscopy data.

Experimental part

We monitored the progress of the reaction by thin layer chromatography (TLC) on Silufol UV 254 plates in hexane-ethyl acetate (4:1) and dichloromethane-isopropanol-acetic acid (20:10:3) solvent systems. Detection of the TLC results was performed under UV light and using an iodine chamber. We determined the content of the main substance in the products by the potentiometric titration method on a laboratory ionometer I-160MI. We measured the melting point on an Electrothermal 1102D Mel-Temp melting point tester. We recorded IR spectra in reflected light on a Spectrum Two PerkinElmer spectrometer at 700-4000 cm^{-1}. We recorded NMR spectra on a Varian UNITY plus instrument with an operating frequency of 400 MHz for DMSO-d_6 solutions at 30 °C. We used the signals of residual solvent protons in ^1H NMR (δH=2.50 m.d.) as a reference for the chemical shifts. We used the signal of tetramethylsilane as a marker.

General methodology for the obtaining of sulfonylureas

6-Methyluracil-5-sulfochloride (2 g, 0.009 mol) is mixed with potassium cyanate (1.12 g, 0.014 mol) and acetonitrile (20 mL). Pyridine (1.53 g, 1.56 mL, 0.019 mol) is added to the obtained suspension under vigorous stirring and stirred at 20-25 °C for 4-5 h (TLC control). Then 0.007 mol of amine **2(a,b)** (2-amino-5-methyl-1,3,4-thiadiazole or 2-amino-5-trifluoromethyl-1,3,4-thiadiazole) is added to the reaction mixture and stirring is continued for another 4-5 h (TLC control). After completion of the reaction, a 70% aqueous solution of acetic acid (2.86 g, 0.048 mol) and 20 mL of water are added dropwise to the resulting mixture. The obtained suspension is filtered after 30 min, the precipitate on the filter is washed with water, dried in air.

1-[(6-methyl-2,4-dioxo-1*H*-pyrimidine-5-yl)sulfonyl]-3-(5-methyl-1,3,4-thiadiazol-2-Yl)urea (4b). Yield is 79%. IR-spectrum, ν/cm^{-1}: 1158, 1328 (SO_2), 1557 (NH), 1677 (C=O), 3444, 3027 (NH). NMR spectrum ^1H (400 MHz, δ, ppm): 2.48 (s, 3H, CH_3); 2.53(s, 3H, CH_3), 6.44(s, 1H, NH); 8.71(s, 1H, SO_2NH); 10.67 (br. s, 1H, NH); 10.94 (br. s, 1H, NH).

1-[(6-methyl-2,4-dioxo-1H-pyrimidine-5-yl)sulfonyl]-3-(5-trifluoromethyl-1,3,4-thiadiazol-2-Yl)urea (4b). Yield is 81%. IR-spectrum, ν/cm^{-1}: 1132 (CF_3), 1131, 1324 (SO_2), 1657 (NH), 1717 (C=O), 3444, 3027 (NH). NMR spectrum ^{1}H (400 MHz, δ, ppm): 2.17 (s, 3H, CH_3), 6.35 (s, 1H, NH); 8.88 (s, 1H, SO_2NH); 10.67 (br. s, 1H, NH); 10.94 (br. s, 1H, NH).

Biological tests

We conducted biotesting of new potential herbicides according to the methodological recommendations by A.S. Golubev [15]. The scheme of the experiment is as follows: 1) control (no treatment – to determine biological efficacy); 2) reference (Rubit and Magnum); 3) solutions of newly synthesised compounds. We performed each variant in triplicate on 100x100 cm plots.

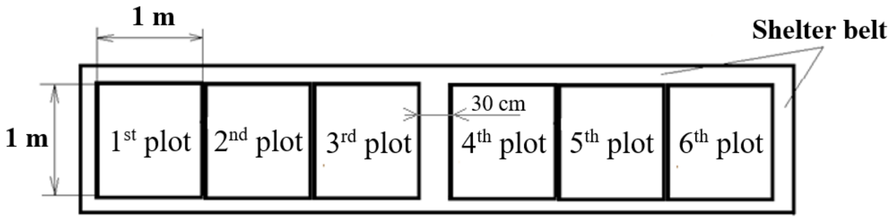


Fig. 3. Total and counted area of plots

We treated weeds in windless weather or in light winds (preferably up to 3 m/s). Since the experimental design involves different concentrations of the same sample, it is initially recommended to spray the plots with the lower application rate first, followed by the plots with the higher concentration. The spraying we conducted by replicates – first all plots of the 1st replicate, then all plots of the 2nd replicate, and so on.

The following evaluations are performed in herbicide efficacy trials:

1) Pre-treatment (quantitative analysis);
2) 7 days after treatment (quantitative analysis);
3) 14 days after treatment (quantitative analysis);
4) 21 days after treatment (weight analysis).

On the 7th day of testing, we recorded changes in the observation objects treated with the Standard and the studied drug: yellowing of the leaves appeared (Table 1).

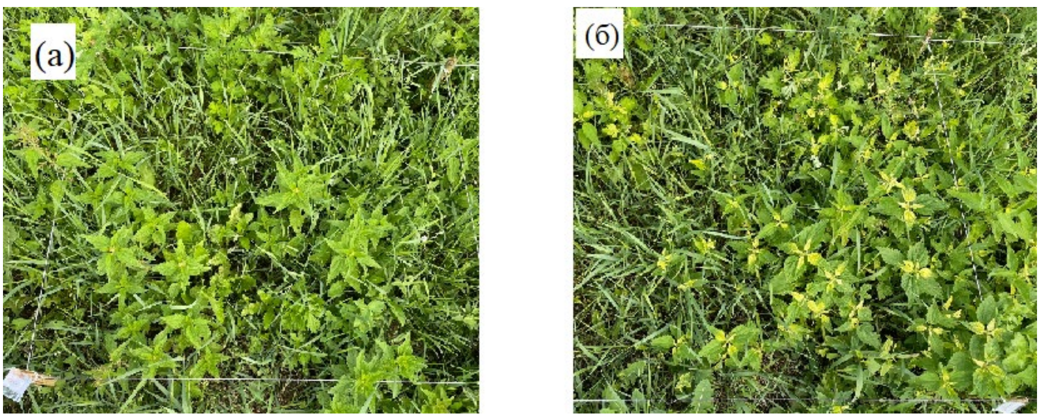
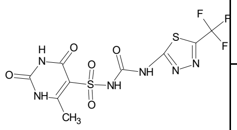
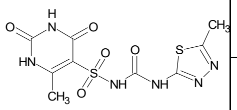


Fig. 4. Photos of the studied plants before the treatment with (**a**) compound **4b** and after the treatment (**b**) compound **4b** after 7 days.

Table 1. Impact of herbicides on total soil weediness (Yaroslavl Oblast, 2024)

Herbicide	Solution concentration	Record dates	Number of weed plants						Weight of weed plants						Biological efficiency of herbicide, %
			Items			Decrease, % of control			g			Decrease, % of control			
			Repeat 1	Repeat 2	Repeat 3	Repeat 1	Repeat 2	Repeat 3	Repeat 1	Repeat 2	Repeat 3	Repeat 1	Repeat 2	Repeat 3	
	800 mg/l	14.07	478	496	473	-	-	-	-	-	-	-	-	-	53.29
		22.07	450	476	449	10.18	0	7.61	-	-	-	-	-	-	
		28.07	409	443	441	16.90	6.14	8.13	-	-	-	-	-	-	
		15.08	115	137	100	76.63	70.47	78.99	852	811	734	51.09	50.49	58.11	
	600 mg/l	14.07	505	487	479	-	-	-	-	-	-	-	-	-	47.23
		22.07	486	469	462	2.99	2.94	11.11	-	-	-	-	-	-	
		28.07	458	450	432	6.91	4.66	10.00	-	-	-	-	-	-	
		15.08	203	191	164	58.74	58.84	65.54	875	940	893	49.77	42.61	46.13	
	800 mg/l	14.07	493	482	509	-	-	-	-	-	-	-	-	-	45..2
		22.07	474	464	489	5.39	2.52	-	-	-	-	-	-	-	
		28.07	444	440	469	9.76	6.78	2.91	-	-	-	-	-	-	
		15.08	142	173	184	71.14	62.72	61.34	886	917	993	49.14	44.02	43.32	
	600 mg/l	14.07	516	479	496	-	-	-	-	-	-	-	-	-	31.92
		22.07	505	466	479	0	2.10	1.44	-	-	-	-	-	-	
		28.07	479	444	456	2.64	5.93	5.00	-	-	-	-	-	-	
		15.08	280	257	299	43.09	44.61	37.18	1163	1128	1203	33.24	31.14	31.34	
Rubit	80 ml/10 l	14.07	498	481	499	-	-	-	-	-	-	-	-	-	60.50
		22.07	462	443	466	7.78	6.93	4.12	-	-	-	-	-	-	
		28.07	426	408	429	13.41	13.56	10.63	-	-	-	-	-	-	
		15.08	77	62	93	84.35	86.64	80.46	701	668	658	59.76	59.22	62.44	
Magnum	2 g / 3 l	14.07	507	486	491	-	-	-	-	-	-	-	-	-	41.00
		22.07	490	470	477	2.20	1.26	1.85	-	-	-	-	-	-	
		28.07	463	445	443	5.89	5.72	7.71	-	-	-	-	-	-	
		15.08	195	208	190	60.37	55.17	60.08	905	1156	967	48.05	29.43	44.81	
Water	-	14.07	506	479	492	-	-	-	-	-	-	-	-	-	-
		22.07	501	476	486	-	-	-	-	-	-	-	-	-	
		28.07	492	472	480	-	-	-	-	-	-	-	-	-	
		15.08	492	464	476	-	-	-	1742	1638	1752	-	-	-	

We calculated the biological effectiveness of herbicides in relation to control using the formula: $E = \frac{K-B}{K\cdot 100}$, where: E is the biological effectiveness of the herbicide, %; K is the number or mass of weeds in the control, examples/m^2 or g/m^2; B is the number or mass of weeds in the herbicide variant, examples /m^2 or g/m^2.

Conclusions

The authors synthesised new sulfonylurea derivatives containing heterocyclic fragments with a yield of 79-81%.

An experiment was conducted on weeds in the village Vyatskoye, Nekrasovsky district, Yaroslavl region, Russia. We introduced samples into the growth and development phase of plants at a rate of 600-800 mg/l. We used the following herbicides as standards: Rubit and Magnum. The reduction in the total number of weeds in the variant with the addition of 600 mg/l of herbicide **4b** was 47.23% (Table 1). An increase in the rate of use of the studied drug to 800 mg / l contributed to an increase in its effectiveness by an average of 6%. The efficiency of applying 800 mg/l of sample **4b** to the growth and development phase was high (up to 53.29%) and exceeded the efficiency of 2g/3l of the Magnum standard. The effectiveness of 800 mg/l of herbicide **4b** was close to the effectiveness level of 80 ml/10 l of the Rubit standard. Studies have shown that newly synthesised herbicides have a significant effect on the growth of weeds. According to a number of indicators, the new herbicides are superior not only to water as a control, but also to the Magnum analogue. Table 1 summarises the results of the field tests.

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