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Authors	Vergush A. Pivazyan, Emma A. Ghazaryan, Armen V. Karapetyan, Roza S. Shainova, Siranush V. Harutyunyan, Asya S. Vorskanyan, Aleksandr P. Yengoyan and Tiruhi A. Gomktsyan
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ORCID® iDs	Armen V. Karapetyan - https://orcid.org/0000-0001-6009-4318; Roza S. Shainova - https://orcid.org/0000-0003-0815-1041; Aleksandr P. Yengoyan - https://orcid.org/0000-0003-4411-4299

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ULTRASOUND-ASSISTED GREEN SYNTHESES OF NOVEL PYRIMIDINE DERIVATIVES AND THEIR COMPARISON WITH CONVENTIONAL METHODS

Vergush A. Pivazyan, Emma A. Ghazaryan, Armen V. Karapetyan, Roza S. Shainova, Siranush V. Harutyunyan, Asya S. Vorskanyan, Aleksandr P. Yengoyan*, Tiruhi A. Gomktsyan

Department for Pesticides Synthesis and Expertise, National Agrarian University of Armenia, Teryan 74, Yerevan, 0009, Armenia

**e-mail: ayengoyan@mail.ru*

Abstract: Ultrasound-assisted green syntheses of novel potentially bioactive pyrimidine derivatives have been carried out. The same compounds were obtained by conventional methods of synthesis, and the reaction times and yields of final products obtained by these two methods were compared. It was found that the time of utrasound-promoted reactions was reduced by almost 6-96 times, and their yields were equal or turn out to be greater compared to the traditional approach. The synthesized compounds showed a pronounced stimulating effect on plant growth. The most active derivatives were selected for deeper biological studies and subsequent field trials.

Keywords plant growth stimulant activity, pyrimidine derivatives, sonochemical synthesis, traditional synthesis

Introduction

Pyrimidine derivatives have a wide diversity of biological activity. The pyrimidine cycle is an integral part of many natural compounds: pyrimidine and purine bases, strong poisons and coenzymes, alkaloids, vitamin B1, riboflavin, folic acid, etc. In medical practice, synthetic antitumor drugs, antibiotics, sulfonamides, barbiturates, as well as antimicrobial, antihypertensive, anthelmintic, antiherpes, antifungal, antiviral, antiparkinsonian, anti-HIV drugs

are used. Some drugs are recommended for infections of the respiratory and urinary tract, peripheral neuropathy, as an expectorant and mucolytic agent.

As a result of ongoing research in the series of substituted pyrimidines, new compounds have been discovered that have antibacterial and antimicrobial [1-4], antifungal [5,6], antitumor [7-9], anti-inflammatory [10,11], anticonvulsant [12,13], antioxidant [14,15], antiviral [16,17], anti-HIV [18-20], anti-tuberculosis [21,22], antimalarial [23-25], cardiotonic [26,27] activity. Some pyrimidine derivatives were inhibitors of acetylcholinesterase [28,29].

In agriculture, pyrimidine derivatives are used as fungicides, insecticides, and acaricides [30]. In recent years, some new pyrimidine derivatives were described that have shown a stimulating effect on plant growth in the experiment [31,32]. However, in general, pyrimidine derivatives are known as herbicides of various chemical groups: pyrimidine diamines, pyrimidineoxybenzylamines, pyrimidinyloxy and pyrimidinylthio derivatives of benzoic acid. In the last 3-4 decades, sulfuroniume derivatives of pyrimidine have become most widespread. In their molecules pyrimidine ring is linked to other heterocycles or an aryl residue through a sulfonylurea group. These drugs are used at very low application rates (10–50 g/ha) and have extremely low toxicity to warm-blooded animals (LD_{50} > 5000 mg/kg) [30].

With prolonged use of chemical plant protection products, pathogens and pests become resistant to the substances used. For this reason, it becomes necessary to systematically replenish their arsenal with new drugs with a different mechanism of action.

In the second half of the 20th century, new fields of chemistry appeared, such as laser chemistry, plasma chemistry, photochemistry, and high-pressure chemistry. In the last 10-15 years, they have been joined by new modern branches: microwave (MW) and ultrasonic (US) chemistry. These methods have a number of advantages, as they allow for high energy savings, a very short period of time to carry out chemical syntheses with higher yields, use water as a solvent, exclude the use of organic solvents, wider use of catalysts, etc., which correspond to the principles of "Green Chemistry".

In sonochemistry, ultrasonic irradiation is used in chemical reactions and processes. The mechanism of this method is due to the acoustic cavitation in liquids.

The aim of this study was the targeted synthesis of novel potentially biologically active pyrimidine derivatives under the action of US irradiation, comparison with conventional methods of synthesis, and investigation of the biological properties of the synthesized compounds in terms of their further practical application.

Results and Disscussion

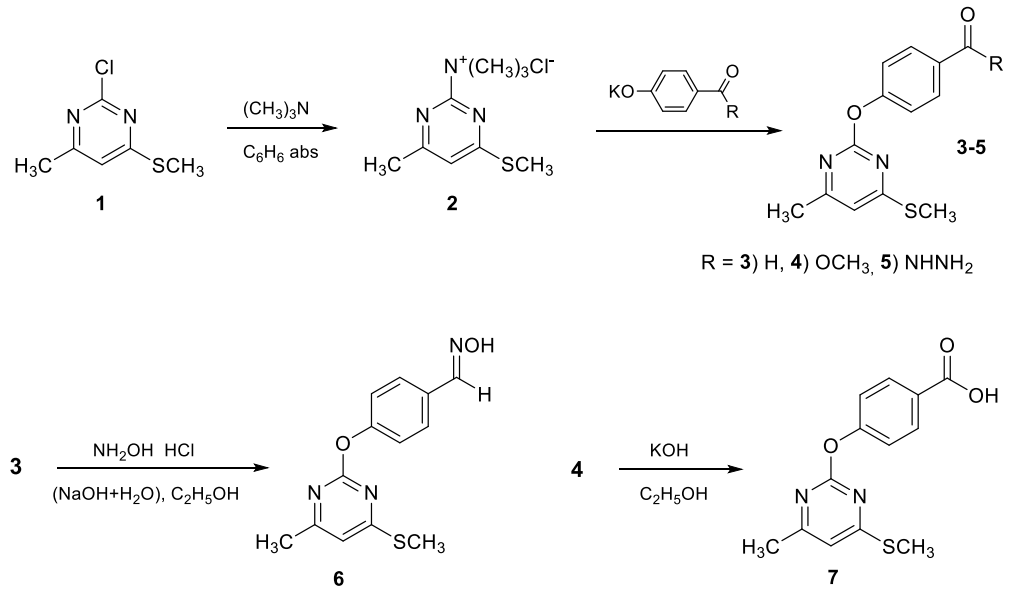
As the starting compound 2-chloro-4-methyl-6-(methylthio)pyrimidine (**1**) was used. The latter is a well-known and widely used basic compound for the synthesis of pyrimidine derivatives. The method described in the literature for the synthesis of 2-chloro-4-methyl-6-(methylthio)pyrimidine (**1**) consists of the following three steps: 1) reaction of methyl 3-oxobutanoate with thiourea in methanol and sodium methylate, 2) methylation of the resulting 4-mercapto-6-methylpyrimidin-2-ol, 3) substitution of the hydroxyl group of the second position of the pyrimidine ring by a chlorine atom. The times of three procedures were 8 h, 12 h and 2 h, respectively. Sonochemical synthesis of compound **1** was carried out using a similar scheme. The yields of these relevant stages were 80% (30 min), 92% (30 min) and 87% (6 min). Thus, the total synthesis time of the starting compound is sharply reduced with an overall high yield of the product (**1**).

During subsequent stages, the conditions of sonochemical syntheses were varied in order to minimize the time of intermediate reactions and achieve the maximum yield of the final product. It turned out that the most optimal conditions were the use of an ultrasonic pulse power of 300 W (30%) and a continuous irradiation time of 30 min.

Practice has shown that the preliminary preparation of the trimethyl-pyrimidinylammonium salt not only greatly facilitates further substitution reactions in the second position of the pyrimidine ring already at room temperature, but also increases the yield of the

target products. For this reason, by reaction of compound **1** with trimethylamine in absolute benzene at room temperature, the corresponding quaternary salt **2** was preliminarily obtained.

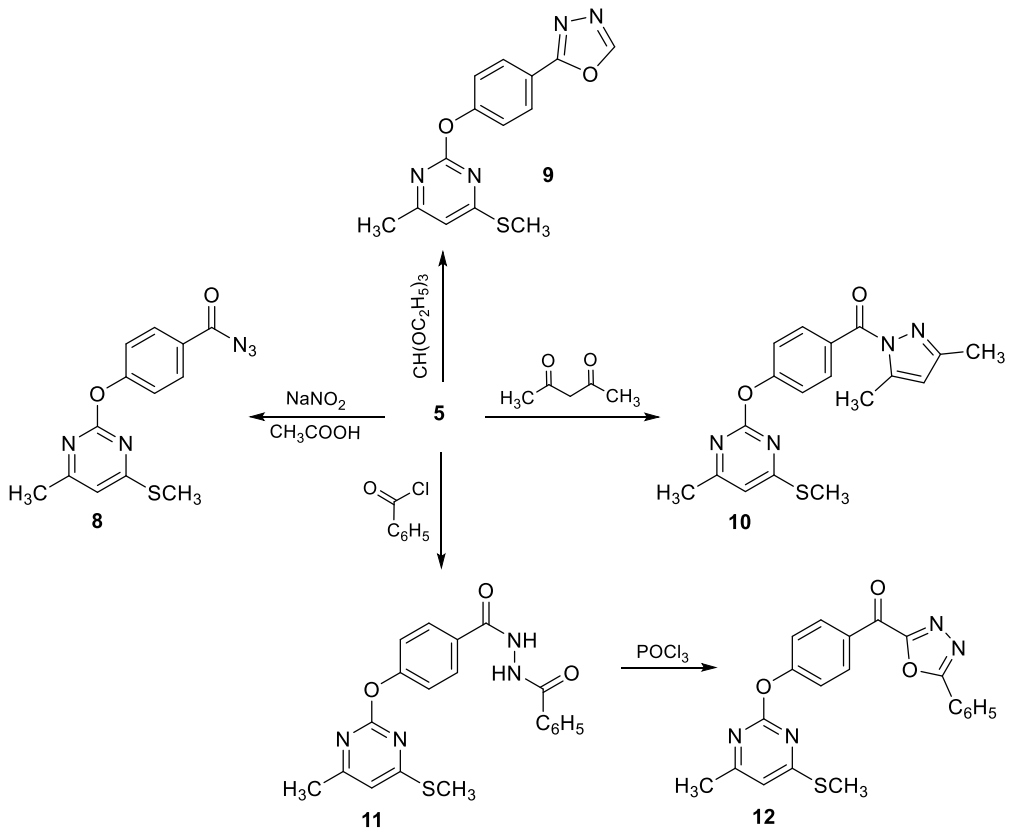
In order to synthesize 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzaldehyde and its oxime, 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy) benzoic acid, as well as its methyl ester and hydrazide, reactions of salt **2** with 4-hydroxybenzaldehyde, methyl ester and hydrazide of 4-hydroxybenzoic acid carried out. However, the reaction yields were rather low (45-50%). For this reason, in order to increase the yield of target products, various sequences of synthetic stages were tried. The highest reaction yields were achieved by implementing the following sequence of chemical steps: first, potassium salts of 4-hydroxybenzaldehyde, methyl ester, and hydroxybenzoic acid hydrazide were synthesized, then they were reacted with quaternary salt **2** (Scheme 1). Further, the reaction of the resulting 4-((4-Methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzaldehyde (**3**) with hydroxylamine hydrochloride in an aqueous solution of NaOH afforded the corresponding oxime (**6**), and methyl 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)-oxy)-benzoate (**4**) with an alcoholic solution of KOH and hydrazine hydrate formed 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzoic acid (**7**) (Scheme 1). With the implementation



Scheme 1: Synthesis of 4-methyl-6-(methylthio)-2-phenoxypyrimidine derivatives

of the specified sequence of stages, the yields of the reactions turned out to be much higher (75-92%).

Some transformations of hydrazide (**5**) have been carried out. Its reaction with sodium nitrite and acetic acid in an aqueous medium the corresponding azide (**8**) was synthesized. As a result of heterocyclization of hydrazide (**5**) with triethoxymethane and pentane-2,4-dione, compounds with a combination of pyrimidine cycle with 1,3,4-oxadiazole (**9**) and pyrazole (**10**) rings in the molecule were formed. The reaction of hydrazide (**5**) with benzoyl chloride afforded *N'*-benzoyl-4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzohydrazide (**11**), the subsequent treatment of latter with phosphorus (V) oxychloride led to (4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)phenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (**12**).

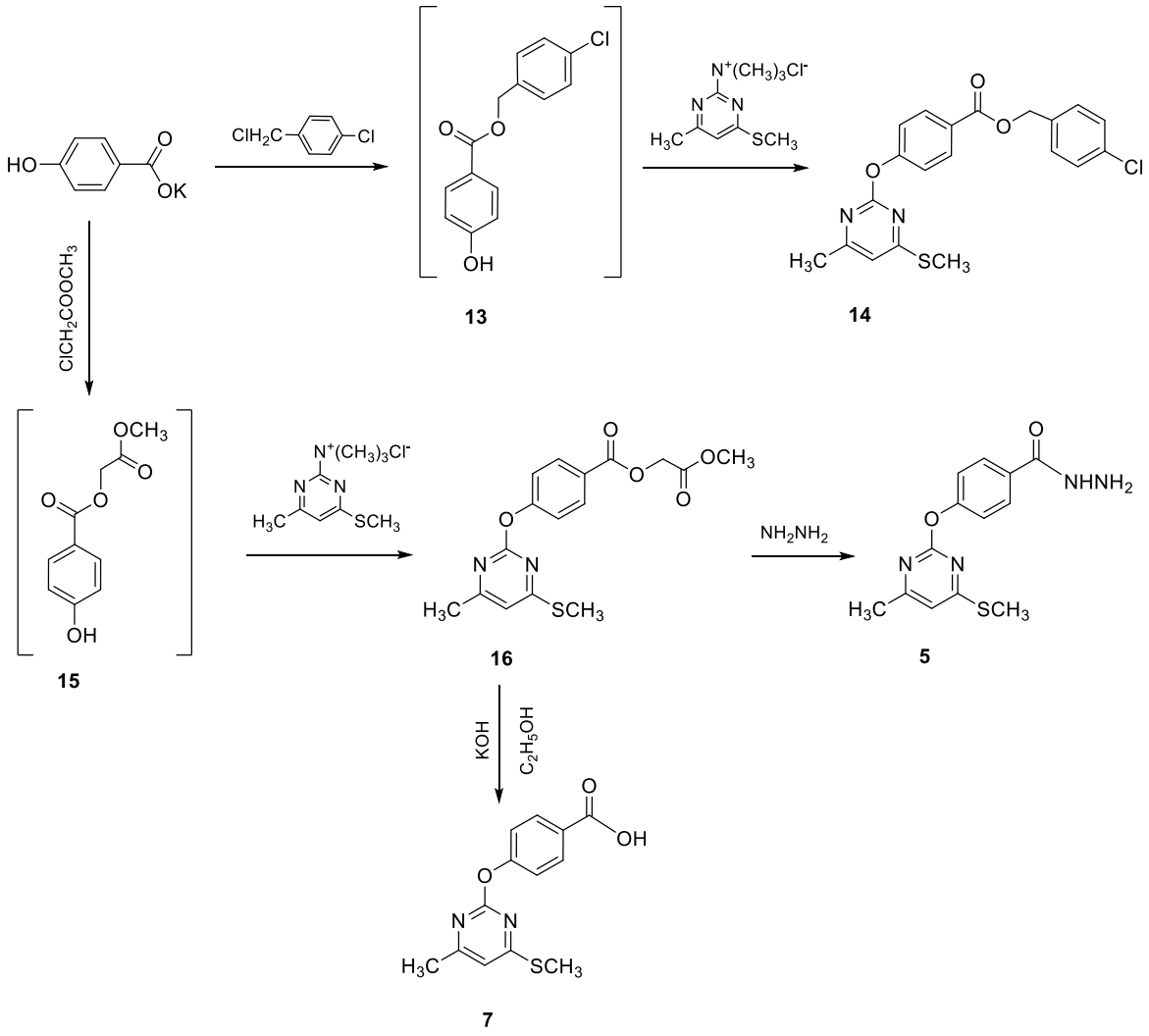


Scheme 2: Transformations of 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzohydrazide (5)

It should be noted that the US-assisted synthesis of compounds **6**, **7** and **12** was not carried out. The US-promoted synthesis of compound **6** failed because the aldehyde was deposited on the ultrasonic generator transducer and was not separated by the addition of alcohol for homogenization. As for compound **7**, the conventional method for its preparation proceeds

rather quickly and in high yield. For this reason, the use of ultrasonic irradiation cannot lead to a significant increase in the efficiency of the synthesis of this compound. The synthesis of compound **12** was not carried out due to the possibility of a negative effect of $POCl_3$ vapor on the generator parts.

The reaction of potassium 4-hydroxybenzoate with 4-chlorobenzylchloride or methyl 2-chloroacetate led to intermediate 4-chlorobenzyl 4-hydroxybenzoate (**13**) and 2-methoxy-2-oxoethyl 4-hydroxybenzoate (**15**). These compounds with quaternary salt (**2**) formed, respectively, 4-chlorobenzyl 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzoate (**14**) and 2-methoxy-2-oxoethyl 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzoate (**16**).



Scheme 3: Synthesis of 4-chlorobenzyl and 2-methoxy-2-oxoethyl 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzoates

To accelerate the synthesis of compounds **14** and **16**, two stages of their preparation from potassium 4-hydroxybenzoate were carried out sequentially without isolating compounds **13** and **15** from the reaction medium. The total synthesis time for final products **14** and **16** was 60 min.

In order to synthesize the corresponding 2-hydrazinyl-2-oxoethyl 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzoate and 2-((4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzoyl)oxy)acetic acid, compound **16** were reacted with hydrazine hydrate (63%) and an alcoholic solution of KOH. However, in both cases, the C(O)–O bond was broken, and 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzohydrazide (**5**) and 4-((4-methyl-6-(methylthio)pyrimidin-2-yl)oxy)benzoic acid (**7**) were obtained. Another route for the synthesis of target products was also tried. First, the reaction of compound **15** with hydrazine hydrate and an alcoholic solution of KOH afforded the corresponding hydrazide and acid, which then reacted with pyrimidine quaternary salt (**2**). However, compounds **5** and **7** were also formed in this case.

Biological properties of synthesized compounds

The obtained compounds were subjected to laboratory vegetation tests to determine herbicidal, fungicidal, growth-regulating properties. Almost all compounds obtained showed a stimulating effect on plant growth. The experiments were carried out on seeds and seedlings of common beans (*Phaseolus vulgaris L*.). The effect of aqueous suspensions of compounds **3**–**16** at concentrations of 25 and 50 mg/L on seed viability, germination, and seedling growth was studied. These data were compared with the effect of heteroauxin solutions of the same concentrations. The activity of the tested compounds varied within 49-90% compared to heteroauxin, the which activity was taken as 100%. In some cases, the growth-stimulating effect of solutions with a lower concentration (25 mg/L) turned out to be higher than that of more concentrated (50 mg/L) solutions. Compounds that showed an activity above 75% in the experiment were selected for deeper study and further field tests using also their solutions with concentrations less than 25 mg/L.

Conclusion

In summary, sonochemical and conventional methods for the synthesis of a series of novel 3-pyrazolyl-6-hydrazinylpyridazine derivatives were carried out. Comparison of these two approaches showed that ultrasonic irradiation sharply reduces the reaction times, and the yields of the final products generally increase. The synthesized compounds during biological screening showed a pronounced stimulating effect on plant growth. The most active of them were selected for deeper study and subsequent field trials.

Experimental

Ultrasonic syntheses were carried out under the action of an ultrasonic generator I10-840. Operating frequency 22 kHz ±10%, maximum pulse power 1000 W. Ultrasonic pulse power of 300 W (30%) and a continuous irradiation time of 30 min were used for the syntheses. The vessel with the reagents that were subjected to irradiation was placed in a water bath, where room temperature (25 ^{o}C) was maintained. The structure of compounds synthesized both by traditional methods and under the action of ultrasonic irradiation was proved by the NMR method. The ^{1}H and ^{13}C NMR spectra were obtained at 30 ^{o}C on a Varian Mercury-300 NMR spectrometer (300 and 75 MHz, respectively) in a mixture of CCl_4/DMSO-d_6 solvents (3:1) using a standard pulse sequence, TMS was used as an internal standard. The following abbreviations were used for singlet, broadened singlet, doublet, triplet, quadruplet, and multiplet NMR signals: s, brs, d, t, q, and m. The progress of the reactions and the purity of the obtained compounds were checked by TLC on Silufol UV-254 plates; an acetone/hexane mixture (2:1 or 1:1) was used as the eluent. Elemental analysis was performed on a Eurovector EA3000 CHN analyzer. Melting points were determined on a Stuart SMP10 apparatus and are uncorrected.

All traditional and ultrasonic syntheses were carried out by the same schemes. Comparison of reaction times, yields and melting points data are shown in Table 1.

Procedures for conventional syntheses of compounds and their spectral data are given in supplementary materials File 1 and File 2.

Table 1: Comparison of US-assisted syntheses of compounds 3-16 with traditional methods

N	US-assisted			Traditional		
	Reaction time* (hour)	Yield (%)	m.p. °C	Reaction time* (hour)	Yield (%)	m.p. °C
3	0.5	90	55-56	4	82	55-56
4	0.5	92	130-131	3	92	130-131
5	0.5	69	170-171	48	75	170-171
6				5	85	155-156
7				2	92	165-166
8	0.3	78	136-137	3	83	136-137
9	0.5	70	140-141	16	65	140-141
10	0.5	87	135-136	24	85	135-136
11	0.5	89	190	4	78	190-191
12				4.5	72	160-161
13	0.5	75	158-160	12	74	158-160
14	2×0.5	91	110-111	30	82	110-111
15	0.5	95	90-91	3	81	90-91
16	2×0.5	82	100-101	30	65	100-101

* Only the reaction time to obtain the final product was taken into account

Supporting Information

Supporting Information File 1: Synthesis of comounds-Experimental

File 2: Characterization data and copies of ^{1}H, ^{13}C NMR spectra

Department for Pesticides Synthesis and Expertise, National Agrarian University of Armenia
Pivazyan Vergush Andranik, ORCID ID: 0000-0002-5900-5119
vergush.pivazyan.50@mail.ru
Ghazaryan Emma Arego, ORCID ID: 0000-0001-8644-2958 emma.ghazaryan.eg@gmail.com
Karapetyan Armen Vardan, ORCID ID: 0000-0001-6009-4318 armkar@inbox.ru
Shainova Roza Sergey, ORCID ID: 0000-0003-0815-1041 rozetta_11@mail.ru
Harutyunyan Siranush Vahagn, ORCID ID: 0000-0002-2962-2028
harutyunyan.siranush70@mail.ru
Vorskanyan Asya Sergey, ORCID ID: 0000-0002-4416-9292 asya.vorskanyan@mail.ru
Yengoyan Aleksandr Paylak, ORCID ID: 0000-0003-4411-4299 ayengoyan@mail.ru
Gomktsyan Tiruhi Avetis, ORCID ID: 0000-0002-2072-8467 tiruhi.gomktsyan@mail.ru

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