

UDC 547.398 + 547.583

<https://www.doi.org/10.34907/JPQAI.2020.98.52.002>

## ANTHELMINTIC ACTIVITY OF MONOSUBSTITUTED AMIDES AND HYDRAZIDES OF 1,4-DICARBOXYLIC ACIDS

**N.V. Kolotova**, *Cand. Sc. Chemistry, Associate Professor of Analytical Chemistry Department, Perm State Pharmaceutical Academy, Perm, Russia, nina.kolotowa2015@yandex.ru*

**A.V. Starkova**, *Cand. Sc. Medicine, Associate Professor of Physiology Department, Perm State Pharmaceutical Academy, Perm, Russia, allaperm@list.ru*

*The anthelmintic activity of 21 derivatives of 1,4-dicarboxylic acids in experiments on earthworms was studied in comparison with the anthelmintic agents such as Levamisole and Pyrantel. It was concluded that phenoxyacetylhydrazide and 4-antipyrilamide of citraconic acid, imidazolylamide and methoxyacetylhydrazide of maleic acid and isonicotinoylhydrazide of phthalic acid have a more pronounced anthelmintic effect in comparison with Pyrantel and the effect of phenoxyacetylhydrazide of citraconic acid is comparable with Levamisole.*

**Keywords:** monosubstituted amides and hydrazides, 1,4-dicarboxylic acids, anthelmintic activity

Helminth infections are among the most common infections in the world and most often affect the poorest and most socially deprived communities. According to the World Health Organization, approximately 1.5 billion people in the world are infected with helminths. According to official data, the incidence of helminthiasis in Russia is about 1%, and children are most often affected by this disease.

The search for compounds with high anthelmintic activity is important, as far as many anthelmintic agents are toxic to humans and cause severe adverse reactions, including

disorders of the gastrointestinal tract (GI), central nervous system (CNS), cardiovascular system (CVS) and hemic system; in addition, their prolonged use often develops insensitivity of helminths to these agents [1,2].

Previously, when studying the anthelmintic activity of a number of 1,4-dicarboxylic acid heterylamides, compounds with an anthelmintic effect were detected, moreover, activity of some compounds exceeded the activity of Levamisole and Pyrantel [3]. For the first time, the anthelmintic effect of 1,4-dicarboxylic acid monohydrazides was studied for derivatives of itaconic and dimethylmaleic acids, but no anthelmintic effect was found [4]. Later, compounds with anthelmintic effect were found among monosubstituted hydrazides of 1,4-dicarboxylic acids [5]. However, anthelmintic activity was studied for a narrow range of 1,4-dicarboxylic acid derivatives.

**The purpose** of this work is to search for compounds with pronounced anthelmintic activity among monosubstituted amides and hydrazides of 1,4 – dicarboxylic acids.

### MATERIALS AND METHODS

The objects of study of biological activity were monosubstituted amides and hydrazides

of succinic, maleic, citraconic, phthalic and tetrachlorophthalic acids, as well as salts of phthalic hydrazide synthesized at the Department of Analytical Chemistry of the Perm State Pharmaceutical Academy using well-known methods [6–9]. The formulas of the studied compounds are shown in the figure

The antihelmintic activity of compounds was studied by the method of M.P. Nikolaev [10] using earthworms 5–8 cm long and 3–5 mm in diameter, purchased in the retail network "Pet Shop" in Perm. 5 ml of 0.5% aqueous solution of the studied compounds was placed and 5 worms were immersed in a Petri dish, then the time of death of each worm was recorded upon the loss of motion activity in response to mechanical irritation. The life time of control worms in purified water is about a day ( $24 \pm 1$  h). As a comparator agent, we used antihelmintic agents such as Pyrantel (Ozon LLC, Russia) and Levamisole (Gedeon Richter, Hungary) with a valid expiration date, purchased in a pharmacy chain.

The experimental results were processed using the Fischer – Student's method of variation statistics [11].

## RESULTS AND DISCUSSION

The anthelmintic activity of 9 monosubstituted amides (compounds 1–9), 10 hydrazides (compounds 10–16, 19–21) and 2 hydrazide salts (compounds 17 and 18) of 1,4-dicarboxylic acids was studied. Two 1,4-dicarboxylic acid heteryl-amides (compounds 5 and 8) showed an antihelmintic effect: maleic acid imidasolylamide (compound 5) and 4-antipyrylamide of citraconic acid (compound 8) are 2 and 1.8 times more active than Pyrantel, respectively. Substitution of an acid fragment in 2-pyrimidylamide of tetrachlorophthalic acid [3] with a maleic acid residue (compound 4) leads to the loss of anthelmintic effect. Among the monosubstituted 1,4-dicarboxylic acid hydrazides, three compounds (14, 16, and 20) with anthelmintic activity were

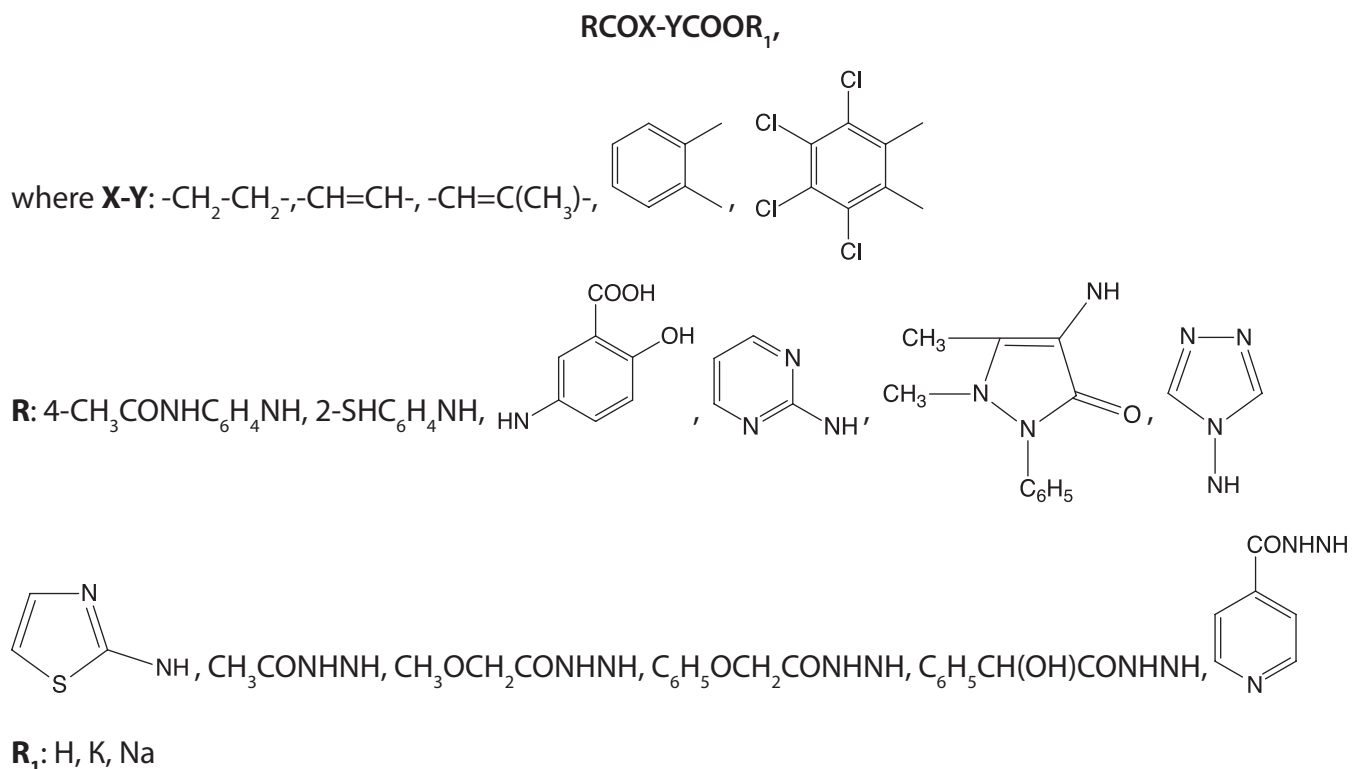


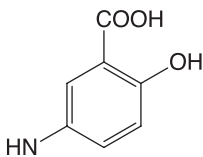
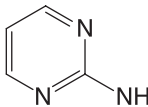
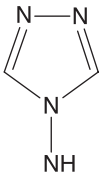
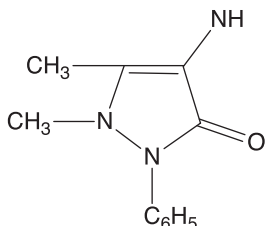
FIG. 1. Chemical formulas of the studied compounds

found. Phenoxyacetylhydrazide of citraconic acid (compound 16) has an anthelmintic effect equal to the action of Levamisole, but a similar derivative of succinic acid (compound 12) does not have anthelmintic activity. The effect of methoxyacetylhydrazide of maleic acid (compound 14) is 2.5 times higher than the effect of Pyrantel, while the same hydrazides of succinic

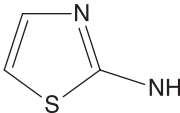
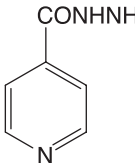
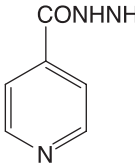
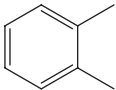
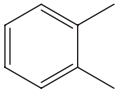
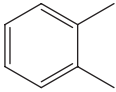
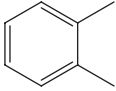
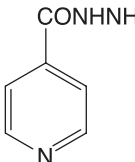
(compound 11) and phthalic (compound 19) acids do not affect the life time of worms. Anthelmintic activity of phthalic acid isonicotinohydrazide (compound 20) is 2 times higher than activity of Pyrantel. Substitution of the phthalic acid residue in this hydrazide with a fragment of succinic acid (compound 13) leads to the loss of activity.

*Tsble*

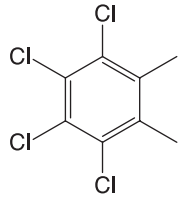
### ANTHELMINTIC ACTIVITY OF MONOSUBSTITUTED AMIDES AND HYDRAZIDES OF SUCCINIC, MALEIC, CITRACONIC, PHTHALIC AND TETRACHLOROPHTHALIC ACIDS

	Compound	X-Y	R	Life time of worms, minutes (experiment)*
1.	4-acetamino-phenyl-amide of succinic acid	-CH <sub>2</sub> -CH <sub>2</sub> -	4-CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub> NH	more than 200
2.	2-thio-phenyl-amid of maleic acid	-CH=CH-	2-SHC <sub>6</sub> H <sub>4</sub> NH	more than 200
3.	3-carboxy-4-hydroxy-phenyl-amide of maleic acid	-CH=CH-		more than 200
4.	2-pyrimidyl-amide of maleic acid	-CH=CH-		more than 200
5.	1-triazolyl-amide of maleic acid	-CH=CH-		101,3±0,67
6.	2-thio-phenyl-amide of citraconic acid	-CH=C (CH <sub>3</sub> )-	2-SHC <sub>6</sub> H <sub>4</sub> NH	more than 200
7.	4-acetyl-phenyl-amide of citraconic acid	-CH=C (CH <sub>3</sub> )-	4-CH <sub>3</sub> COC <sub>6</sub> H <sub>4</sub> NH	more than 200
8.	Antipyril-amide of citraconic acid	-CH=C (CH <sub>3</sub> )-		121,0±9,99

Продолжение таблицы

	Compound	X-Y	R	Life time of worms, minutes (experiment)*
9.	2-thiazolyl-amide of citraconic acid	-CH=C (CH <sub>3</sub> )-		more than 200
10.	Acetyl-hydrazide of succinic acid	-CH <sub>2</sub> -CH <sub>2</sub> -	CH <sub>3</sub> CONHNH	more than 200
11.	Methoxy-acetyl-hydrazide of succinic acid	-CH <sub>2</sub> -CH <sub>2</sub> -	CH <sub>3</sub> OCH <sub>2</sub> CONHNH	more than 200
12.	Phenoxy- acetyl-hydrazide of succinic acid	-CH <sub>2</sub> -CH <sub>2</sub> -	C <sub>6</sub> H <sub>5</sub> OCH <sub>2</sub> CONHNH	more than 200
13.	Iso-nicotinoyl-hydrazide of succinic acid	-CH <sub>2</sub> -CH <sub>2</sub> -		more than 200
14.	Methoxy-acetyl-hydrazide of maleic acid	-CH=CH-	CH <sub>3</sub> OCH <sub>2</sub> CONHNH	85,4±10,32
15.	Iso-nicotinoyl-hydrazide of maleic acid	-CH=CH-		more than 200
16.	Phenoxy- acetyl-hydrazide of citraconic acid	-CH=C (CH <sub>3</sub> )-	C <sub>6</sub> H <sub>5</sub> OCH <sub>2</sub> CONHNH	18,5±2,97
17.	Sodium salt of phthalic acetyl-hydrazide		CH <sub>3</sub> CONHNH	more than 200
18.	Potassium salt of phthalic acetyl-hydrazide		CH <sub>3</sub> CONHNH	more than 200
19.	Phthalic methoxy-acetyl-hydrazide		CH <sub>3</sub> OCH <sub>2</sub> CONHNH	more than 200
20.	Phthalic iso-nicotinoyl-hydrazide			104,7±10,90

Окончание таблицы

	Compound	X-Y	R	Life time of worms, minutes (experiment)*
21.	Hydroxyphenyl acetyl-hydrazide of tetrachlorophthalic acid		C <sub>6</sub> H <sub>5</sub> CH (OH) CONHNH	more than 200
Comparator agents			Pyrantel	215,0±0,37
			Levamisole	20,2±2,08

Note: \* – the life time of control worms was about a day (24±1 h)

## CONCLUSION

1. The anthelmintic activity of 21 1,4-dicarboxylic acid derivatives was studied using a model with earthworms. Five compounds (phenoxy-acetyl-hydrazide and 4-antipyrilamide of citraconic acid, imidazolyl-amide and methoxy-acetyl-hydrazide of maleic acid, phthalic acid iso-nicotinoyl-hydrazide) showed more pronounced anthelmintic activity in the experiment in comparison with an anthelmintic agent such as Pyrantel.

2. Anthelmintic activity of phenoxy-acetyl-hydrazide of citraconic acid is comparable with effect of Levamisole.

## REFERENCES

1. Polyakov V.E., Lysenko A.Ya. *Helminthiases of children and adolescents*. – M.: Medicine, 2003. – 256 p.
2. Lukshina R.G., Lokteva M.M., Pavlikovskaya T.N. Under the general editorship of R.G. Lukshina. *Human parasitic diseases: Monograph*. – 2nd ed., revised and amended. – H.: Publishing house "INJEK". 2005. – 472 p.
3. Kolotova N.V., Starkova A.V. Anthelmintic activity of heteryl amides of 1,4-dicarboxylic acids // *Development and registration of medicines*. – 2017. – №1 (18). – pp. 136–138.
4. Kolotova N.V., Starkova A.V., Chashchina S.V. *Synthesis and biological activity of monosubstituted itaconic and dimethylmaleic acid hydrazides // Issues of ensuring the quality of medicines*. – 2016. – №3 (13). – pp. 15–23.
5. Kolotova N.V., Starkova A.V. *Biological activity of 1,4-dicarboxylic acids aroyl hydrazides // Development and registration of medicines*. – 2017. – №2 (19). – pp. 167–170.
6. Dolzhenko A.V., Kolotova N.V., Kozminykh V.O. and others. *Substituted amides and hydrazides of dicarboxylic acids. Message 14\**. *Synthesis, antimicrobial and anti-inflammatory activity of 4-antipyril-amides, 2-thiazolyl-amides and 1-triazolyl-amides of certain dicarboxylic acids // Journal of Pharmacy and Chemistry*. – 2003. – Vol. 37. -№3. – pp. 42–44.
7. Kolotova N.V., Kozminykh E.N., Kolla V.E. and others. *Substituted amides and hydrazides of 1,4-dicarboxylic acids. Message 7\**. *Synthesis and pharmacological activity of some acyl hydrazides of maleic, succinic and phthalic acids // Journal of Pharmacy and Chemistry*. – 1999. – Vol. 33. – №5. – pp. 22–28.
8. Dolzhenko A.V., Kolotova N.V., Kozminykh V.O. and others. *Substituted amides and hydrazides of dicarboxylic acids. Message 15\**. *Synthesis*

- and hypoglycemic activity of some amides and acyl hydrazides of tetrachlorophthalic acid // Journal of Pharmacy and Chemistry. – 2003. – Vol. 37. – №4. – pp. 186–188.*
9. Kolotova N.V., Skvortsova N.L., Kozminykh V.O. and others. *Synthesis of biologically active acyl hydrazides of maleic, succinic and phthalic acids // The manuscript of the department of VINITI 29.09.1997. №2940-B97. – Perm. – 1997. – pp. 1–31.*
10. Nikolaev M.P. *Experimental bases of pharmacology and toxicology. Practical guideline / M.P. Nikolaev. – Moscow-Leningrad: Medgiz. 1941. – 195 p.*
11. Prozorovsky, V. V., *Statistical processing of the results of pharmacological studies / V.V. Prozorovsky // Psychopharmacology and biological narcology. – 2007. – Vol. 7. Issue 3–4. – pp. 2090–2120.*