Химические науки

PREDICTION OF BIOLOGICAL ACTIVITY AND TOXICITY OF 5-DIETHOXYPHOSPHORYL-4-ETHOXY-5-ETHOXYCARBONYL-2 – (1-IMINO) ETHYLTHIO-4,5-DIHYDROTHIAZOLE AND ITS DERIVATIVES

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The biological activity of 5-Diethoxyphosphoryl-4-ethoxy-5-ethoxycarbonyl-2-(1-imino)ethylthio-4,5-dihydrothiazole was analyzed by PASS (Prediction of Activity Spectra for Substances) and toxicity by GUSAR (General Unrestricted Structure-Activity Relationships).

Methods of obtaining these substances:

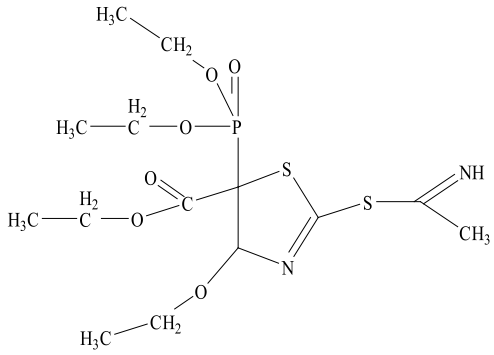
1. 5-Diethoxyphosphoryl-4-ethoxy-5-ethoxycarbonyl-2 – (1-imino)ethylthio-4,5-dihydrothiazole. One solution of thiocyanate acetal (3.83 g, 0.0 l mol) and thioacetamide (0.75 g, 0.01 mol) in absolute acetonitrile or ethanol (30 ml) was heated with a reverse refrigerator for 16 hours. the solvent was removed in vacuum and 10 ml of 3:1 ether-acetone was added to the resulting oil. The yellow crystalline precipitate was filtered and dried to yield 2.31 g (56%) of the compound.

To determine the potential biological activity chose the program PASS, which is based on the analysis of dependencies structure-activity. Pa and Pi are presented as estimates of the measure of the substance belonging to the classes of active and inactive compounds, respectively. The larger the value ofPa for a particular activity and the smaller the value ofPi, the greater the chance to detect this activity in the experiment. Forecasts of biological activity of compounds are given in table 1.

As can be seen from table 1, it can be said that both compounds exhibit different inhibitory properties.

Further, the forecast of acute toxicity of the studied compound was carried out using the software product GUSAR (General Unrestricted Structure-Activity Relationships) presented in tables 2 and 3.

1.



2.

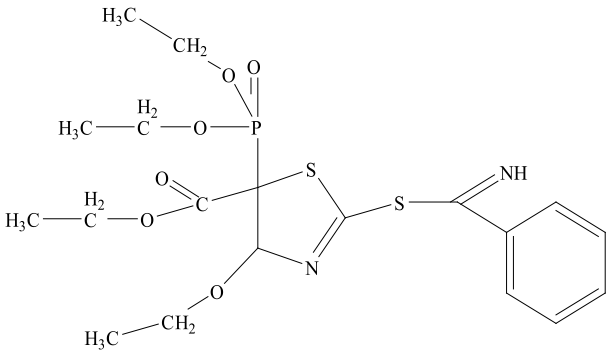


Table 1

Prediction of biological activity based on the results of the PASS program 1

1.

Pa	Pi	Activity
0,795	0,015	Mannotetraose inhibitor of 2-alpha-N-acetylglucosaminyltransferase
0,666	0,024	Supplementfactor d inhibitor
0,607	0,009	Inhibitorkokolina
0,648	0,068	Inhibitor of CDP-glycerol-glycerol phosphotransferase
0,613	0,039	An inhibitor of glutamate-5-polulegendarnaya
0,567	0,024	Inhibitor of N-acetylneuraminate 7-O (or 9-O) – acetyltransferase
0,579	0,054	Inhibitor of 5-O – (4-coumaroyl) – D-hinata 3' – monooxygenase
0,584	0,059	Sugarphosphataseinhibitor
0,503	0,004	Stimulatorofboneformation
0,507	0,020	Generalanesthesia
0,541	0,060	Treatment of acute neurological disorders

2.

Pa	Pi	Activity
0,747	0,021	Mannotetraose inhibitor of 2-alpha-N-acetylglucosaminyltransferase
0,645	0,028	Supplementfactor d inhibitor
0,598	0,032	Arginine-2-monooxygenase inhibitor
0,587	0,043	An inhibitor of glutamate-5-polulegendarnaya
0,543	0,014	Inhibitorkokolina
0,606	0,081	Inhibitor of CDP-glycerol-glycerol phosphotransferase
0,515	0,019	Generalanesthesia
0,556	0,061	Inhibitor of 5-O – (4-coumaroyl) – D-hinata 3' – monooxygenase
0,495	0,005	Paraoxonasesubstrate
0,546	0,058	Treatment of acute neurological disorders
0,525	0,048	Venomininhibitor AB
0,545	0,069	Sugarphosphataseinhibitor
0,494	0,033	Inhibitor of N-acetylneuraminate 7-O (or 9-O) – acetyltransferase
0,456	0,005	Stimulatorofboneformation

Table 2

Prediction of acute toxicity in rats using the GUSAR software product 1

1.

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,539 in AD	-0,873 in AD	-0,024 in AD	-0,329 in AD
Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
119,400 in AD	55,230 in AD	390,300 in AD	193,400 in AD

2.

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
-0,311 in AD	-0,927 in AD	0,487 in AD	-0,047 in AD
Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
231,900 in AD	56,080 in AD	1457,000 in AD	425,500 in AD

Table 3

Acute classification of rodent toxicity by chemicals by OECD project using GUSAR software product 1

1.

Rat IP LD50 Classification	Rat IV LD50 Classification	RatOral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 4 in AD

2.

Rat IP LD50 Classification	Rat IV LD50 Classification	RatOral LD50 Classification	Rat SC LD50 Classification
Class 4 in AD	Class 4 in AD	Class 4 in AD	Class 4 in AD

From table 3 it can be concluded that the toxicity of both compounds is low, 4 hazard classes.

Thus, the results obtained by predicting the biological activity using the PASS program, and the toxicity of the studied compounds using the GUSAR software product allow us to conclude that compound 1 is more active than 2, and the toxicity of both compounds is equal. Therefore, compound 1 has a higher potential activity, and this compound can be used prospectively for further laboratory studies.

References

1. Poroikov V.V. Computer prediction of biological activity of substances: limits of the possible. Chemistry in Russia, 1999. No. 2. P. 8-12.

2. Asadov H.A., Huseynov F.I., Mikhailov G.G., Valiullina R.J. Moscow, 2009, Chemistry of heterocyclic compounds. 2001. vol. 45. number 7. P. 878.

ОСНОВНЫЕ ПОДХОДЫ К ИЗУЧЕНИЮ СТАРЕНИЯ ЧЕЛОВЕКА

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На протяжении многих веков люди пытались выяснить причины старения, безрезультатно искали эликсир молодости. Но и в наши дни биология и химия процесса старения мало изучены. Учёные разных стран проводят эксперименты по увеличению продолжительности человеческой жизни [3].

В «Программе ООН по исследованиям старения в XXI столетии», принятой Второй Всемирной ассамблеей ООН, отмечается [4]