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Predictive and experimental determination of antioxidant activity in the series of substituted 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones

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Abstract.

Calculations for the determination of the most active radical-binding compounds in the series of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones were carried out using the PASS Online computer prediction method. Antioxidant activity with respect to DPPH was studied experimentally by a photometric method. It was found that 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones, having in their composition methoxy and methyl substituents possess the greatest antioxidant activity. The presence of a nitro group in the structure of the compound contributes to a decrease in antioxidant activity.

Keywords: antioxidant activity, antiradical, anti-radical, DPPH, PASS Online, pyrrol-2-ones, spectrophotometry

INTRODUCTION

Oxidation is one of the vital biochemical processes. The most basic substrates for these processes are lipids and carbohydrates from nutrition and oxygen from atmosphere. Adverse by-products - free radicals also form in a result of these processes. To minimize the harm they can cause one can apply special substances antioxidants. That is why search and synthesis of new antioxidants is of a great interest for researchers in chemistry, pharmacy and biology.

Some synthetic antioxidants have good potential. Among them derivatives of isoquinoline [1], benzimidazole [2], benzotriazole [3], benzofuran [4], benzothiazole [5], 1,2,4-triazole [6-8], thiazole [9], triazoline [10, 11], coumarin [12-14], piperazine [15, 16], triazine [17], pyrrole [18-20], indole [21-24], dihydropyridine [25], pyridinone [26], dihydrofuran [27], oxazolidine [28], thiourea [29-31], uracil [32], organophosphorus compounds and phosphorylated heterocycles [33-35], metal-organic complexes [36-46], chitosan derivatives [47-50] , substituted phenols and polyphenols [51-54] and other compounds have been studied closely.

The spectrophotometric determination of formed radicals of 2,2-diphenyl-2-picryl-1-hydrazyl (DPPH) is one of the most commonly used methods for assessing antioxidant activity. The DPPH radical is considered to be a stable free radical due to delocalization of electrons of the whole molecule, thus demonstrating that the molecule is not dimerized. Delocalization of electrons occurs in a radical form, which has a violet color in the visible region of the spectrum, possessing a maximum absorption at 517 nm (in methanol solution).

The DPPH binding method makes it possible to use it for screening of compounds – radical "assemblers" ("scavengers") possessing antiradical activity, and quantify the significance of the antiradical mechanism in the overall antioxidant activity [55, 56].

The effectiveness of screening of compounds with high biological and physiological activity is facilitated by such prediction software programs as PASS (Prediction of Activity Spectra for Substances) [57, 58], OCHEM [59] and many others. In order to theoretically estimate the radical binding activity of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones using the PASS Online software, we calculated the probability of this mechanism in the following variants: Radical Scavenger, Oxygen Scavenger, Nitric Scavenger and Radical Formation Agonist.

The use of computer prediction precedes detailed experimental verification of biological activity of compounds, which is associated with significant expenses of material and time resources. The PASS Online prediction software allows to analyze more than 4000 types of biological activity of compounds of a diverse chemical structure and is designed to provide a more rational approach to the synthesis of compounds with given activity types [60].

MATERIALS AND METHODS

4-(2,2-Dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones (**1–21**) with antimicrobial, nootropic, antitumor, anti-inflammatory activity [61–68] were synthesized as a result of reaction of pivaloyl pyruvic acid and arylidenylamines according to the procedure [61]. Design of obtained compounds is present in **Fig.** and **Table**. The optical density was measured with the use of KFK-3-01 photoelectric colorimeter. The commercially available 2,2-diphenyl-2-picryl-1-hydrazyl (DPPH) and tris(hydroxymethyl)aminomethane (THAM) from Sigma Aldrich as well as high-purity dimethylsulfoxide (DMSO) and methanol were used.

The predicted antioxidant activity $\mathbf{P_a}$ for synthesized compounds was calculated using the PASS Online [69] software, taking values from 0 (min possible activity) to 1 (max possible activity).

The 3 ml of 0,3 mmol solution of DPPH in methanol, 1 ml of THAM-HCl buffer solution with pH = 7,4 were added to a

solution of $2x10^{-5}$ mol of the test substance (**1–21)** or reference standards in DMSO. The solution was held at room temperature (25^{o}C) for 30 minutes, and then its optical density was measured at a wavelength of 517 nm in cells with an absorbing layer thickness of 0,5 cm. The same solutions were used as the comparison solution, but without the test substance. Known antioxidants were used as standards of antioxidant activity: Resveratrol, Mexidol and Trolox.

The antioxidant activity Q (%) was calculated as the loss of DPPH radicals according to the formula:

$$Q = \frac{100\,(D_0 - D_x)}{D_0}$$

where D_0 is the optical density of the comparison solution, D_x is the optical density of the DPPH solution in the presence of the test substance or the standard of antioxidant activity.

The obtained measurements were processed in a standard way using the Student's t-test (the confidence probability was 0,95).

Analysis of the predicted ($\mathbf{P_a}$) and experimental (**Q**) activities showed that the majority of compounds exhibit a moderate antioxidant activity, while compound **3** having methyl substituents possess antioxidant activity approaching the standard of antioxidant activity, Trolox [67, 68], and compound **14**, for which antioxidant activity was calculated by the software with a probability of more than 50%, does not possess such a high ability to bind radicals.

CONCLUSION.

It was found that 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones, having in their composition methoxy and methyl substituents possess the largest radical-binding activity. The presence of a nitro group in the structure of the compound contributes to a decrease in antioxidant activity. Studies have shown the prospects of searching for new compounds having antioxidant activity in the series of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones.

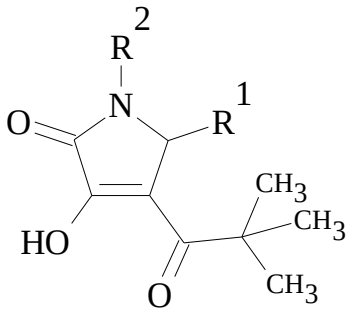

Figure 1

Table. Structure and antioxidant activities of 4-(2,2-dimethylpropanoyl)-3-hydroxy-1,5-diphenyl-1,5-dihydro-2*H*-pyrrol-2-ones

Compound	R^1	R^2	Decrease of radicals (Q), %	Prediction of activity (P_a)
1	C_6H_5	C_6H_5	20,11 ± 1,07	0,370
2	4-$CH_3C_6H_4$	C_6H_5	35,65 ± 0,93	0,346
3	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	72,86 ± 3,24	0,354
4	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$	61,14 ± 1,93	0,322
5	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	19,10 ± 0,94	0,301
6	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	68,49 ± 3,78	0,316
7	4-BrC_6H_4	4-$CH_3C_6H_4$	46,18 ± 2,29	0,298
8	4-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	12,43 ± 0,97	0,335
9	4-BrC_6H_4	4-$NO_2C_6H_4$	23,90 ± 2,71	0,306
10	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	31,61 ± 3,8	0,335
11	4-$NO_2C_6H_4$	C_6H_5	7,28 ± 0,62	0,306
12	4-$(CH_3)_2NC_6H_3$	2-pyrydyl-	34,99 ± 2,67	0,276
13	4-BrC_6H_4	4-$CH_3OC_6H_4$	23,75 ± 1,44	0,296
14	4-$NO_2C_6H_4$	4-$C_2H_5OC_6H_4$	24,19 ± 1,35	0,586
15	4-FC_6H_4	4-$CH_3C_6H_4$	36,53 ± 1,93	0,298
16	4-$CH_3OC_6H_4$	C_6H_5	27,47 ± 2,06	0,315
17	4-$NO_2C_6H_4$	2-pyrydyl-	55,83 ± 0,64	0,335
18	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	65,94 ± 2,31	0,316
19	4-ClC_6H_4	4-$CH_3C_6H_4$	52,80 ± 1,15	0,283
20	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	38,04 ± 2,76	0,332
21	4-$CH_3C_6H_4$	2-naphtyl-	16,28 ± 0,89	0,273
Standards:				
Resveratrol			80,42 ± 0,73	
Mexidol			36,90 ± 0,71	
Trolox			82,56 ± 0,20	

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