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Antiradical activity and bioprediction of *o*- and *p*-hydroxybenzoic acid hydrazide derivatives

This article provides results of evaluation of synthesized biologically active substances 1–4 antiradical activity according to their ability to interact with the 2,2- diphenyl-1-picrylhydrazyl radical (DPPH•). It was found that all synthesized compounds 1–4 have antiradical activity. Pronounced antiradical activity was shown by N-ethyl-2-(2-hydroxybenzoyl)hydrazine-carbothioamide (1) (IC_{50}(DPPH) = 12.5 μM) and N-ethyl-2-(4-hydroxybenzoyl)hydrazine-carbothioamide (2) (IC_{50}(DPPH) = 16.7 μM) samples under the conditions of this test system. Activity of N-ethyl-2-(2-hydroxybenzoyl) hydrazinecarbothioamide (1) and N-ethyl-2-(4-hydroxybenzoyl)hydrazinecarbothioamide (2) samples are comparable to activity of known antioxidants. Studied substances 1 and 2 are promising for further advanced research of their antioxidant properties and other types of biological activity. Results of PASS computer system applicability estimation for prediction of biological activity using structural formula as a part of pre-experimental screening are provided. Expected activity of chemical compounds combines physiological activity of initial hydrazides of *o*- and *p*-hydroxybenzoic acids as well as components of structural molecule. According to bioprediction data analysis, all compounds can act as inhibitors with a high degree of probability.

Keywords: antioxidant, antiradical activity, free radical, thiosemicarbazide, 1,2,4-triazole, DPPH, bioprediction, PASS.

Introduction

Antioxidants have found widespread practical application in chemistry, chemical engineering, food industry and pharmacy. Multiple contributions are provided on research of various natural compounds [1–4], their synthetic analogues [5–12] and botanicals extracts [13–15] antioxidative activity. Antioxidative therapy is a way of treating various diseases which develop significantly through free-radical processes [16, 17]. Antioxidants are implemented in therapy of various pathologies including inflammatory processes [18–20] and cardiovascular diseases [21, 22]. They are uses as adaptogens in stress conditions [23] and for treatment of neurodegenerative disorders, such as Alzheimer's and Parkinson disease as well as cognitive dysfunction.

In recent years there has been search and streamlined synthesis of new multifunctional phenol type antioxidants superior in their efficiency to existing analogues considering peculiarities of structure and antioxidative activity interrelation. A promising area of highly effective antioxidants creation is synthesis of «hybrid molecules» combining several functional groups reacting independently or synergistically to substrates oxidation process in lipidic or water phase.

The purpose of this paper is to research the anti-radical activity of synthetic compounds 1–4 in reference to 2,2-diphenyl-1-picrylhydrazyl (DPPH), and expand the synthetic antioxidants based on hydrazides of *o*- and *p*-hydroxybenzoic acids.

Experimental

For studied samples 1–4 antiradical activity estimation in test with DPPH radical methanol solution of DPPH (100 μM) was used. For selection of substances with pronounced antiradical activity 2 ml of 100 μM DPPH methanol solution was mixed with 20 ml of researched substance dissolved in methanol in 5 mM concentration. This way, the final concentration of test sample in reaction mixture was 50 μM. Optical density reduction at 515 nm was measured 10 minutes after adding test sample to DPPH solution. Interaction with the DPPH radical was carried out at final concentrations of 50, 25, 20, 15, 10, 5 and 2.5 μM for studied substances

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that can reduce the optical density more than 50 %. Then, the test sample concentration that can reduce the optical density by 50 % (IC_{50}(DPPH)) was determined.

Computer prediction of biological activity was carried out using PASS software which predicts 4000 types of biological activity based on training array analysis containing structural formulas and biological activity data of more than 300,000 chemical compounds. Structural formulas of studied compounds are entered into system as files of Mol or SDF format. Prediction results are calculated as compound probability of displaying certain biological activity (Pa) and probability of not displaying such activity (Pi). PASS system is thoroughly described in works [24–26] http://www.way2drug.com/passonline website provides resource allowing to predict more than 4000 types of biological activity.

Results and Discussion

Previously we have synthesized hydrazide derivatives of *o*- and *n*-hydrobenzoic acids (1–4) [27–29] which contain thioamide group, ethyl unit and 1,2,4-triazole groups. 1–4 compounds antiradical properties estimation for the purpose of revealing active antioxidants was carried out for the first time.

Several series of experiments were carried out to define antiradical properties according to technique [30]. DPHH radical and test sample solution optical density are shown in Table 1.

Table 1

Optical density of 100 μM DPPH radical with 50 μM examined substance solution after 10 minute incubation period

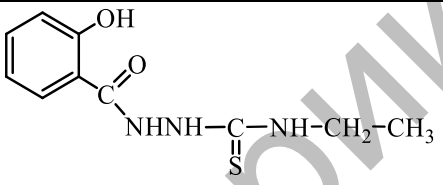
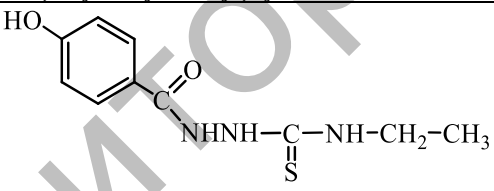
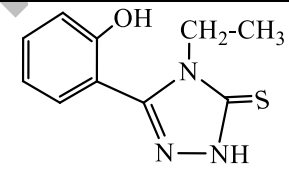
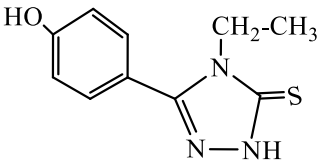
No.	Structural formula and substance name	Optical density, rel. unit
1	 N-ethyl-2-(2-hydroxybenzoyl)hydrazine-carbothioamide (1)	0.112
2	 N-ethyl-2-(4-hydroxybenzoyl)hydrazine-carbothioamide (2)	0.127
3	 3-(2-hydroxyphenyl)-4-ethyl-1*H*-1,2,4-triazol-5(4*H*)-thione (3)	0.587
4	 3-(4-hydroxyphenyl)-4-ethyl-1*H*-1,2,4-triazol-5(4*H*)-thione (4)	0.418
5	Control (DPPH solution without test sample)	0.852

Table 1 shows that all 1–4 compounds are capable of antiradical activity, compounds 3 and 4 are able to reduce optical density below 50 %, so from all compounds 1–4 only compounds 1 and 2 are promising for further research.

Second series of experiment was carried out to study ability of compounds 1 and 2 to interact with DPPH radical at various concentrations (from 2.5 to 50 μM) (Table 2, Fig. 1).

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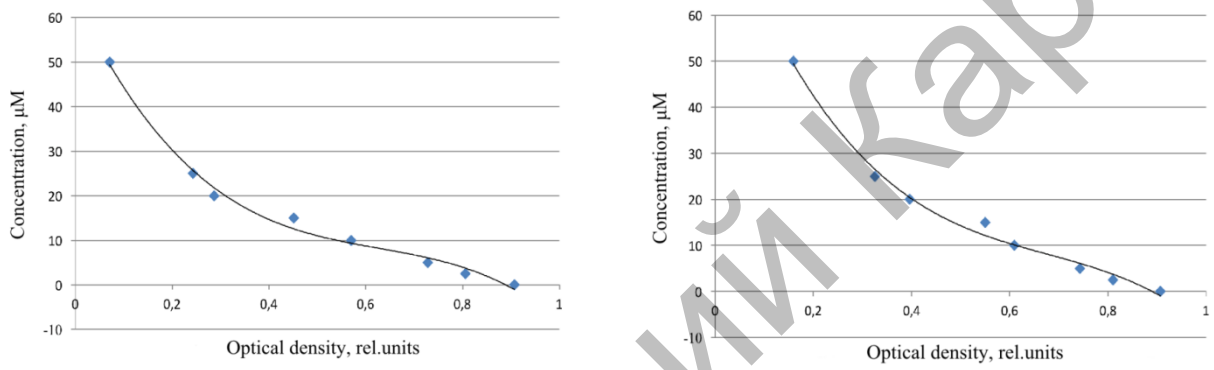
Table 2

Optical density of DPPH radical 100 μM with test sample 1 and 2 solution at final concentrations 50, 25, 20, 15, 10, 5 and 2.5 μM after 10 minute incubation

No.	Final concentration of substances 1 and 2 in the reaction mixture, μM	Optical density, rel. unit	
		reaction mixture of compound 1	reaction mixture of compound 2
1	50	0.071	0.159
2	25	0.243	0.325
3	20	0.287	0.396
4	15	0.451	0.55
5	10	0.57	0.609
6	5	0.728	0.743
7	2.5	0.806	0.810
	Control (DPPH solution without test sample)	0.907	0.907



a) *b*)

Figure 1. Dependence of optical density of the reaction mixture compound 1 (*a*) and compound 2 (*b*) on the concentration

Using created calibration curves (Fig. 1) concentrations of N-ethyl-2-(2-hydroxybenzoyl)-hydrazinecarbothioamide (1) and N-ethyl-2-(4-hydroxybenzoyl)hydrazinecarbothioamide (2) were determined. Estimation of 1–4 compounds antiradical activity towards DPPH radical showed that in conditions of given test system samples 1 and 2 displayed the most pronounced antiradical activity. The concentration of samples 1 and 2 to be able to reduce optical density of DPPH radical 100 μM solution by 50 % was found. IC_{50}(DPPH) for compound 1 is 12.5 μM, IC_{50}(DPPH) for compound 2 is 16.7 μM.

Referring to the data, the IC_{50}(DPPH) for the standard ascorbic acid sample is 19.9 μM. 1 and 2 samples activity is competitive with ascorbic acid reference sample.

According to reference data [31, 32] IC_{50}(DPPH) (μM) for known antioxidants is the following: glutathione — 49, hydrochinone — 27, trolox — 28, α-tocopherol — 28, quercetin — 8. This way, antiradical activity of samples 1 and 2 is comparable to that of known antioxidants. Studied substances 1 and 2 are promising for further research of their antioxidative properties. Experimentally received results allow for the conclusion about practicability of further research in order to search for prospective antioxidant compounds among derivatives of *o*- and *p*-hydroxybenzoic acids are reasonable.

According to Chemical Abstract Service data, nowadays there are more than 65 million known chemical compound structures, while amount of those virtually generated *in silico* but not synthesized yet exceeded 165 billion [33, 34]. Despite widespread use of high performance screening methods, it is not possible to experimentally test millions of compounds to define their biological activity. This in one of fundamental issues of contemporary chemistry — research of «structure-activity» correlations of physiologically active compounds [35, 36]. Due to this, a very important component of modern approaches to research and development of new bioactive substances are information technologies which allow reducing amount of substances researched in biological experiments and streamline patterns of their research. One of the ways of using information technologies for searching bioactive substances is computer-assisted bioactivity prediction through chemical structure.

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In order to define compounds 1–4 expected biological activity we have carried out bioprediction using one of the most effective contemporary software — PASS (Prediction of Activity Spectra for Substances) (Table 3), which is used to define «structure-activity» correlations. Result of expected activity for compounds 1–4 is shown in Table 3.

Table 3

Results of a computer bioprediction of the expected type of biological activity of compounds 1–4

Comp. No.	Probability	Ranging	Activity type names
1	0.846	0.003	Gonadotropin antagonist
	0.815	0.004	HMGCS2 expression enhancer
	0.814	0.011	Taurine dehydrogenase inhibitor
	0.802	0.002	PfA-M1 aminopeptidase inhibitor
	0.769	0.004	Catechol oxidase inhibitor
	0.760	0.004	Antituberculosic
	0.727	0.005	Antimycobacterial
	0.725	0.005	Ovulation inhibitor
2	0.857	0.005	Taurine dehydrogenase inhibitor
	0.847	0.003	Gonadotropin antagonist
	0.819	0.004	HMGCS2 expression enhancer
	0.792	0.003	PfA-M1 aminopeptidase inhibitor
	0.739	0.003	Trimethylamine dehydrogenase inhibitor
	0.725	0.004	Antituberculosic
	0.744	0.038	Mucomembranous protector
3	0.839	0.007	Arylacetonitrilase inhibitor
	0.827	0.004	Histidine kinase inhibitor
	0.772	0.005	Gamma-guanidinobutyraldehyde dehydrogenase inhibitor
	0.751	0.009	Proteasome ATPase inhibitor
	0.748	0.012	Glutathione thiolesterase inhibitor
	0.725	0.005	Aminobutyraldehyde dehydrogenase inhibitor
	0.718	0.003	Alkaline phosphatase inhibitor
4	0.881	0.005	Arylacetonitrilase inhibitor
	0.824	0.005	Glutathione thiolesterase inhibitor
	0.812	0.004	Gamma-guanidinobutyraldehyde dehydrogenase inhibitor
	0.799	0.005	Proteasome ATPase inhibitor
	0.797	0.008	Muramoyltetrapeptide carboxypeptidase inhibitor
	0.782	0.004	Sulfite reductase inhibitor
	0.755	0.007	Peroxidase inhibitor
	0.751	0.011	NADPH-cytochrome-c2 reductase inhibitor
	0.740	0.004	Aminobutyraldehyde dehydrogenase inhibitor
	0.715	0.013	2-Hydroxyquinoline 8-monooxygenase inhibitor
	0.747	0.049	Aspulvinone dimethylallyltransferase inhibitor
	0.715	0.018	Ribulose-phosphate 3-epimerase inhibitor
	0.712	0.015	UDP-N-acetylglucosamine 4-epimerase inhibitor
	0.701	0.012	Fatty-acyl-CoA synthase inhibitor

Compounds 1–4 bioprediction data analysis suggests that the compounds can display inhibitive, antimicrobial and antitubercular activity with a high degree of probability. PASS system provides comparable antitubercular activity probability for compounds 1 and 2 (Pa = 0.760 and Pa = 0.725), compound 2 can display antimicrobial activity (Pa = 0.727). Compounds 1–4 can act as various inhibitors with probability (Pa > 0.7). Compounds 3 and 4 are highly likely to be enzyme inhibitors.

Data of computer-assisted biological activity prediction from PASS online computer system require further experimental research and validation but provide opportunity for dedicated research of specific biological activity types which have quite high probability of experimental displaying. This way, prediction data can be taken to plan further experimental studies in test systems of *in vitro* and *in vivo*.

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Conclusions

1. All synthesized compounds have anti-radical activity, but compounds 1 and 2 have pronounced anti-radical activity. The activity of samples 1 and 2 is not inferior to the reference sample of ascorbic acid. The IC_{50}(DPPH) for ascorbic acid is 19.9 μM. The IC_{50}(DPPH) for N-ethyl-2-(2-hydroxybenzoyl)hydrazinecarbothioamide (1) is 12.5 μM, and IC_{50}(DPPH) for N-ethyl-2-(4-hydroxybenzoyl)hydrazinecarbothioamide (2) is 16.7 μM. The researched substances of 1 and 2 are perspective for an in-depth study of their antioxidant properties.

2. The prediction data can be taken to plan further experimental studies in test systems of *in vitro* and *in vivo*.

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о- және *п*-гидроксибензой қышқылының гидразид туындыларының радикалға қарсы белсенділігі мен биоболжамы

Мақалада биологиялық белсенді заттардың 2,2-дифенил-1-пикрилгидразил (ДФПГ, DPPH•) радикалымен әрекеттесу қабілеті бойынша радикалға қарсы белсенділікті бағалау нәтижелері келтірілген. Осы тест-жүйе жағдайында N-этил-2-(2-гидрокси-бензоил)гидразинкарботиоамид (1) және N-этил-2-(4-гидроксибензоил)гидразинкарботиоамид (2) үлгілері радикалға қарсы белсенділікті көрсеткені және олардың біріншісі IC_{50}(DPPH) = 12.5 μM, екіншісі IC_{50}(DPPH) = 16.7 μM-ға тең екендігі айқындалды. Зерттелген 1–4 қосылыстардың ішінде тек 1 мен 2 қосылыстарының оксиданттқа қарсы қасиеті мен биоактивтіліктің басқа түрлерін одан әрі терең зерттеуге перспективалы болып табылады. PASS компьютерлік бағдарламаны қолдана отырып, тәжірибелік алдын-ала скрининг кезеңі ретінде құрылымдық формула бойынша биологиялық белсенділікті болжау үшін пайдалану мүмкіндігінің бағалау нәтижелері келтірілген. Химиялық қосылыстардың күтілетін белсенділігі *о*- және *п*-гидроксибензой қышқылдарының бастапқы гидразидтерінің физиологиялық белсенділігі мен құрылымдық молекуланың құрамдас бөліктерін біріктіреді. Биоболжамның талданған мәліметтерінен, барлық қосылыстардың ингибитор ретінде болу мүмкіндігі үлесі жоғары.

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Кілт сөздер: антиоксидант, радикалға қарсы белсенділік, бос радикал, тиосемикарбазид, 1,2,4-триазол, ДФПГ, биоболжам, PASS.

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Антирадикальная активность и биопрогноз производных гидразидов *о*- и *п*-гидроксибензойных кислот

В статье приведены результаты оценки антирадикальной активности синтезированных биологически активных веществ 1–4 по способности взаимодействовать с радикалом — 2,2-дифенил-1-пикрилгидразилом (ДФПГ, DPPH•). Установлено, что все синтезированные соединения обладают антирадикальной активностью, но в условиях данной тест-системы выраженную антирадикальную активность проявили образцы N-этил-2-(2-гидроксибензоил)гидразинкарботиоамида (1) IC_{50}(DPPH) = 12,5 μM, для N-этил-2-(4-гидроксибензоил)гидразинкарботиоамида (2) IC_{50}(DPPH) оказалось равной 16,7 μM. Активность образцов N-этил-2-(2-гидроксибензоил)гидразинкарботиоамида (1) и N-этил-2-(4-гидроксибензоил)-гидразинкарботиоамида (2) сопоставима с активностью известных антиоксидантов. Поэтому из синтезированных соединений 1–4 соединения 1 и 2 перспективны для дальнейшего углубленного изучения их антиоксидантных свойств и других видов биоактивности. Приведены результаты оценки возможности использования компьютерной системы PASS для прогнозирования биологической активности по структурной формуле как этапа доэкспериментального скрининга. Предполагаемая активность химических соединений комбинирует как физиологическую активность исходных гидразидов *о*- и *п*-гидроксибензойных кислот, так и составляющих компонентов структурной молекулы. Из анализа данных биопрогнозирования все соединения с высокой степенью вероятности могут выступать в качестве ингибиторов.

Ключевые слова: антиоксидант, антирадикальная активность, свободный радикал, тиосемикарбазид, 1,2,4-триазол, ДФПГ, биопрогноз, PASS.

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