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The synthesis, characterization, antioxidant and antimicrobial activity of some novel amides of the esters of substituted 1,4-dihydropyridines

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Abstract: The esters of substituted 1,4-dihydropyirdines (1,4-DHP) are formed in the reaction of an appropriate aldehyde and ethyl acetoacetate in the presence of concentrated water solution of ammonia. The esters form the amides by the reaction with primary amines. The series of the amides has been synthesized with the aim to analyze their chemical characteristics, antioxidant and antimicrobial activity. The amine used in this research is 2-aminothiazole. The antioxidant activity is analysed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) methods and the antimicrobial activity screening was performed by broth microdilution method, using different microbial strains. The characterization of the obtained amides was done by melting points, FTIR, NMR and elemental analysis. The possibilities for further research was suggested, which could lead to the application of selected compounds.

Keywords: biologically active compounds; DPPH analysis; ABTS analysis; broth microdilution method.

INTRODUCTION

The derivatives of substituted 1,4-dihydropyirdines (1,4-DHP), such as esters (Fig. 1), have lately drawn attention because of their significant biological activity.

Various medicines containing the esters of substituted 1,4-DHP are used as calcium antagonists, or cardiovascular agents (antihypertensive drugs) as it is stated in literature[1] by Debache *et. al*. Furthermore, the interest for the various

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derivatives of 1,4-DHP becomes even greater because of its similarity to nicotinamide dinucleotide, the coenzyme which is involved in a lot of metabolic processes.

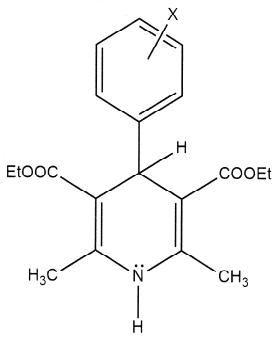

Fig. 1. The general formula of substituted esters of 1,4-DHP.

The methods for the synthesis of the esters of 1,4-DHP originate from 1882 when Hantzsch developed his synthesis.[2] By today the variations of the method mentioned above have been created, depending on the demand for the production speed and yield.

As it is mentioned already, this group of compounds is known as the active compounds of the medicines for the calcium channel blocking and for the insufficient heart activity. The aim of the therapy in which the drugs based on them are used is to provide reliable and healthy work of the body muscles, especially of the heart muscle[3] and also as vasodilators.[4]

The amide bond is among the most significant functional groups in chemistry and biochemistry, a part of protein and peptide molecules and also a part of an active substance of many medicines[5] and 1,4-DHP molecule is an usual base for it.

The antioxidant activity of the 1,4-DHP derivatives has already been examined.[6,7] Ahamed *et.al.*[8] synthesized 18 amides of the esters 1,4-DHP with the aim to study their antimicrobial and anticoagulant activity, using differently substituted esters of 1,4-DHP and 3 amines: 2-amino-4-phenylthiazole, 5-phenyl--1,3,4-tiadiazole-2-amine and 5-phenyl-1,3,4-oxadiazole-2-amine. The products synthesized from chlorophenyl and nitrophenyl esters of 1,4-DHP, with 2-amino--4-phenylthiazole displayed significant activity against *Escherischia coli* and *Candida albicans*, respectively. (Fig. 2a and b).[8] Furthermore, the amide with the hydroxyphenyl substituent, synthesized with 5-phenyl-1,3,4-tiadiazole-2-amine showed rather prominent anticoagulant activity in comparison to the referent compound heparine (Fig.2c).[8]

Based on this study,[8] the synthesis of amides of the esters substituted 1,4--DHP was performed in this research. The amine used was 2-amino-thiazole (Fig. 3).

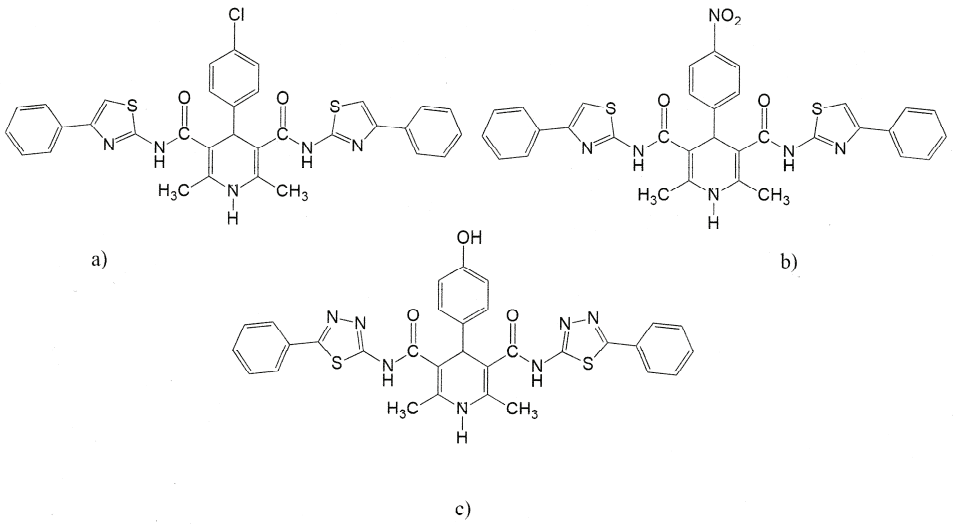

Fig. 2. The formulas of synthesized amides of the esters of 1,4-DHP.[8]

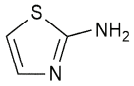

Fig. 3. The formula of 2-aminothiazole.

Substituted 2-aminothiazoles can be used as base reactants for the synthesis of biocides, fungicides, dyes and medicines for the treatment of hyperthyroidism.[9]

EXPERIMENTAL

The synthesis of esters 1,4-DHP[6]

The reaction mixture of 0.01 mole of the aldehyde which was used, 0.02 mol of ethyl acetoacetate, 0.01 mol of concentrated water solution of ammonia and 20 mL of methanol was refluxed for 6 h with mixing, at 65 °C (Fig. 4). After that, the mixture was poured into the beaker and intensively stirred at room temperature. It was then left overnight to crystallise. The obtained white crystals were washed in methanol and recrystallised in the same solvent. The list of the synthesized compounds is given in Table I.

Synthesis of the amides of the esters 1,4-DH[8]

The mixture of each of the esters of 1,4-DHP (0.005 mole) and 2-aminothiazole (0.01 mol) was dissolved in ethanol and then kept for 5 min in an ultrasonic bath. It was afterwards washed by distilled water and recrystallised from ethyl acetate. The reaction scheme is presented in Fig. 4 and the list of synthesized compounds is given in Table II.

DPPH assay[16]

The examined amides were diluted in DMSO in 10 different concentrations. A stable free radical DPPH$^{\bullet}$ (Fluka Chemie AG Buchs) was diluted in methanol, at the concentration of 6.58×10^{-5} M. 140 μL of DPPH$^{\bullet}$ solution was poured into 96 wells on the microtiter plate, as well as 110 μL of DMSO solutions of tested compounds and also pure DMSO (10 μL) as control specimen. It was left for 30 min in the dark, at room temperature and then the absorb-

ance at 517 nm was measured using Shimadzu 1700 UV–Vis spectrophotometer. All measurements were repeated 3 times. Ascorbic acid was used as reference substance in the concentrations from 50 up to 500 mg mL^{-1}. IC_{50} was calculated based on the percentage of neutralised DPPH•.

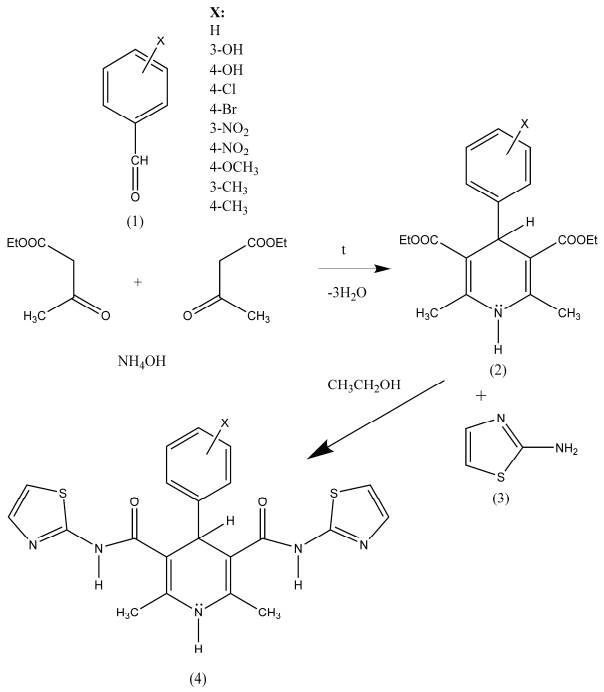

Fig. 4. The synthesis of the amides of the esters of 1,4-DHP (**4**) with 2-aminothiazole (**3**) *via* esters of 1,4-DHP (**2**) that are produced from the corresponding substituted benzaldehydes (**1**).

TABLE I. The synthesized esters of 1,4-DHP

No.	Compound	X
1a[10]	4-Phenyl-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	H
2a[11]	4-(3'-Hydroxyphenyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	3-OH
3a[12]	4-(4'-Hydroxyphenyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	4-OH
4a[10]	4-(4'-Chlorophenyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	4-Cl
5a[13]	4-(4'-Bromophenyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	4-Br
6a[11]	4-(3'-Nitrophenyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	3-NO_2
7a[10]	4-(4'-Nitrophenlyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	4- NO_2
8a[10]	4-(4'-Metoxyphenyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	4-OCH_3
9a[14]	4-(3'-Methylphenyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	3-CH_3
10a[15]	4-(4'-Methylphenyl)-2,6-dimethyl-3,5-dicarboetoxy-1,4-dihydropiridine	4-CH_3

ABTS assay[17]

Bisradical cation $ABTS^{\bullet+}$ was obtained by the reaction of potassium persulfate (2.5 mM) and ABTS (7 mM) of 16 h in the dark. After $ABTS^{\bullet+}$ was stabilised, it was diluted by meth-

anol up to the absorbance of 0.700±0.02 at 734 nm, measured using Shimadzu 1700 UV–Vis spectrophotometer. Then 20 μL of each specimen (solutions of 3 mmol L^{-1} of tested compounds in DMSO) was added into 2 mL of the prepared $ABTS^{\bullet+}$ solution and the noted above absorbance was measured. The solution of ABTS with 20 μL was used as control specimen. Ascorbic acid was used as a reference substance and the antioxidant activity of the tested compounds was compared to it. IC_{50} was calculated based on the percentage of neutralised $ABTS^{\bullet+}$.

TABLE II. The synthesized amides of the esters of 1,4-DHP

No.	Compound	X
1b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-phenyl-3,5-pyridinedicarboxamide	H
2b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(3-hydroxyphenyl)-3,5-pyridinedicarboxamide	3-OH
3b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(4-hydroxyphenyl)-3,5-pyridinedicarboxamide	4-OH
4b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(4-chlorophenyl)-3,5-pyridinedicarboxamide	4-Cl
5b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(4-bromophenyl)-3,5-pyridinedicarboxamide	4-Br
6b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(3-nitrophenyl)-3,5-pyridinedicarboxamide	3-NO_2
7b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(4-nitrophenyl)-3,5-pyridinedicarboxamide	4-NO_2
8b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(4-metoxyphenyl)-3,5-pyridinedicarboxamide	4-OCH_3
9b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(3-methylphenyl)-3,5-pyridinedicarboxamide	3-CH_3
10b	1,4-Dihydro-2,6-dimethyl-N^3,N^5-bis(2-thiazolyl)-4-(4-methylphenyl)-3,5-pyridinedicarboxamide	4-CH_3

In vitro *antimicrobial activity*[18]

The antimicrobial activity of all synthesized compounds was determined on a wide range of different microorganisms by broth microdilution method.[12] The advantage of this method is its capability to quantitatively determine antimicrobial activity and gives precise insight into the effect of every examined compound on the applied bacterial strains.

The broth microdilution method[18] was applied to determine the minimal inhibitory concentrations (*MIC*) of the investigated compounds against nine American Type Cell Collection (ATCC) bacterial strains and one strain of yeast, *Candida albicans* (Table III). The method was performed in agreement with Clinical and Laboratory Standard Institute (CLSI 2005).

The active microbial cultures were prepared from lyophilized standard strains by transferring them to test tubes with the appropriate broth. The nutrient broth was used for bacterial strains, except for *L. monocytogenes*, for which the soya tryptone broth was used.

The malt broth was used for *C. albicans.* All bacterial strains were incubated for 24 h at 37 °C while *C. albicans* was incubated at 32 °C. The density of microbial suspensions was set approximately at 10^5 CFU (colony forming units), using the appropriate broth.

TABLE III. The examined bacteria and fungi types

No.	Microorganism	ATCC No.
1	*Staphylococcus aureus* (G+)	6538
2	*Lysteria monocytogenes* (G+)	19115
3	*Enterococcus faecalis* (G+)	29212
4	*Shigella sonnei* (G–)	29930
5	*Salmonella enteritidis* (G–)	13076
6	*Yersinia enterolitica* (G–)	27729
7	*Escherichia coli* (G–)	35150
8	*Proteus hauseri* (G–)	13315
9	*Pseudomonas aeruginosa* (G–)	27853
10	*Candida albicans*	10259

All examined compounds were first dissolved in 5 % dimethyl sulfoxide to the concentration of 2.5 mg mL^{-1}, and then series of concentrations were prepared by two-fold dilution, using the appropriate broth. The serial concentrations were prepared directly in microtiter plates and the final volume of specimens was 50 μL. The investigated concentrations were in the range from 0.0024 to 1.25 mg mL^{-1}. In the last column only the appropriate broth was added. Then 50 μL of each microbial suspension were added in each well, so that the final concentrations of the examined extracts were half of those at the beginning, and the final volume was 100 μL in each well. Triphenyltetrazoliumchloride (TTC), in concentration of 0.75 vol. % was used as the growth indicator. If the growth of the microbial strain occurs, this indicator gives the rosy-red colour to the broth. The plates with bacteria were incubated at 37 °C, and with *C. albicans* on 32 °C, for 24 h. The results were read the following day and for *MIC* value of each compound on every strain was taken the concentration at which there was no development of red colour. All tests were performed in triplicate and the *MIC* values were constant.

Characterization of synthesised compounds.

FTIR spectra were recorded on Thermo Scientific Nicolet iS10, elemental analysis was done on Vario EL III CHNOS and ^{1}H- and ^{13}C-NMR were recorded on Bruker Ascend 400 MHz (^{1}H 400 MHz, ^{13}C 100 MHz). The resulting data are given in Supplementary material to this paper.

RESULTS AND DISCUSSION

Antioxidant activity – DPPH

Based on the interaction of the synthesized compounds with the DPPH free radical the capability of a compound to transfer a hydrogen atom can be determined. The greater above-mentioned capability the compound possess the higher antioxidant activity it has. The stability of DPPH radical is based on the analysed compound structure and the solvent which is used. The results of the DPPH test for 10 analysed amides of the esters of 1,4-DHP are given in Table IV, in the form of IC_{50} values. The relationship between the structure of the examined compounds and their antioxidant activity can be related to the present substituents on the aromatic ring and their position. Some of the compounds showed con-

siderable antioxidant activity, namely the one with the 3-OH group (**2b**) displays the most prominent activity, while the 4-OH (**3b**) compounds show it also, but it is somewhat weaker. Furthermore **3b** displayed even lower activity than **2b**, which points to the effect of shifting the position of OH group along the aromatic ring, in other words the increase of its distance from the side chain decreases the antioxidant activity. Apart from the OH-substituted derivatives, the only one with certain, but considerably weak antioxidant activity is the 4-NO_2 (**7b**) one and all the rest of them showed no activity, according to DPPH method.

TABLE IV. IC_{50} values of the analysed compounds determined by DPPH method

Compound	IC_{50} / mM
1b	–
2b	0.578
3b	1.377
4b	–
5b	–
6b	–
7b	1.848
8b	–
9b	–
10b	–

Antioxidant activity – ABTS

The same amides were examined by ABTS test and the results are displayed in Table V.

TABLE V. The results of the ABTS antioxidant activity of the analysed compounds

Compound	IC_{50} / mM
1b	2.95
2b	1.21
3b	1.25
4b	-
5b	2.65
6b	-
7b	2.5
8b	-
9b	-
10b	-

The strongest antioxidant activity by the ABTS method was again shown in the case of OH-substituted compounds, in the same order (from the stronger **2b** to the weaker **3b**), and even slighter for the 4-NO_2 compound (**7b**), confirming the previously used DPPH method. However, when ABTS method is used, some activity is also detected for the unsubstituted derivative **1b** and the 4-Br derivate-

ive (**5b**), which does not show activity with DPPH. It can be concluded that ABTS method is more sensitive to the antioxidant activity for the examined type of compound.

Antimicrobial screening

Only some amides showed considerable activity against the tested strains of microorganisms, mostly the same which had also shown antioxidant activity, but also the unsubstituted amide. Hydroxyl substituted amides (**2b** and **3b**) proved to be the most active against both G+ (*S. aureus*, *L. monocytogenes*) and G– bacterial strains (*S. sonnei*, *Y. enterolytica*, *P. hauseri)*, but not as well against *C. albicans*. The unsubstitued amide **1b** displayed some activity towards G– (*S. sonnei*, *Y. enterolytica)* and rather a weak one against G+ (*L. monocytogenes*) and *C. albicans*. 4-Br (**5b**) showed some activity against G+ (*S. aureus*, *L. monocytogenes*) and 4-NO_2 only some against *S. aureus.*

The overall results of the antimicrobial screening are given in Table VI.

TABLE VI. Antimicrobial activity of examined compounds (mM)

Cmpd.	Microbe									
	S. aureus	*L. monocytogenes*	*E. faecalis*	*S. sonnei*	*S. enteritidis*	*Y. enterolytica*	*E. coli*	*P. hauseri*	*P. aeruginosa*	*C. albicans*
1b	4.44	1.80	4.55	0.79	5.10	0.87	5.25	1.22	2.35	1.18
2b	0.18	0.36	2.54	1.24	2.54	0.58	2.54	0.62	5.10	2.44
3b	0.21	0.41	2.64	1.38	2.72	0.62	2.82	0.75	5.12	2.81
4b	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06
5b	0.63	0.98	5.12	3.01	5.12	0.77	3.05	1.02	5.12	4.45
6b	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06
7b	0.89	1.12	3.07	2.72	2.95	0.88	3.01	1.11	3.89	2.99
8b	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06
9b	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06
10b	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06	>5.06

Overall activity can be described as weak to moderate against G+ or G– strains of bacteria, or yeast *C. albicans.* The activity cannot be specified as selective towards G+ or G– strains, as it is not very strong however the obtained data can be used to direct the further investigation.

CONCLUSIONS

The synthesized amides were characterized by FTIR, NMR, melting points and elemental analysis (the data are given in Supplementary material). The antioxidant activity was analysed by two similar methods, DPPH and ABTS. When DPPH method was used it was shown that the hydroxyphenyl substituted compounds were the most efficient. Some weaker activity was also displayed by the 4-nitrophenyl substituted derivative, while 3-nitrophenyl derivative and the unsubstituted compound showed no antioxidant activity at all. In agreement with

that, the ABTS method also displayed the hydroxyphenyl substituted derivatives as active and the 4-nitrophenyl derivative as weakly active, but also detects some slight activity in the case of the 4-bromo substituted compound, which makes this method more suitable for further analysis, when the antioxidant activity of the given type of compound is examined.

The results of antimicrobial screening were moderately significant and pointed to the compounds with antioxidant activity as well.

The conclusion can be derived that the amides of the hydroxyl substituted esters of 1,4-dihydropyridines should be considered for further research and that perhaps some attention should be paid to nitro and halogen substituted also.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12635, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА, КАРАКТЕРИЗАЦИЈА, АНТИОКСИДАТИВНА И АНТИМИКРОБНА АКТИВНОСТ НЕКИХ НОВИХ АМИДА ЕСТАРА 1,4-ДИХИДРОПИРИДИНА

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Естри супституисаних 1,4-дихидропиридина се формирају у реакцији одговарајућег алдехида и етил-ацетоацетата у присуству амонијум-хидроксида. Наведени естри прелазе у амиде реакцијом са примарним аминима. Серија оваквих амида је синтетисана са циљем да се испита њихова антиоксидативна и антимиркобна активност, као и хемијске карактеристике. Амин употребљен за синтезу је 2-аминотиазол. Антиоксидативна активност је анализирана DPPH и ABTS методама, а антимикробна бујон микродилуционом методом. Карактеризација добијених једињења урађена је помоћу тачака топљења, FTIR, NMR и елементалном анализом. Предложене су могућности за наставак истраживања, који бу водио њиховој примени одређених испитиваних једињења.

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