Bulgarian Chemical Communications, Special Issue E, (pp. 68 – 73) 2017

Synthesis and radical scavenging activity of cinnamic acid esters

M. Chochkova[1]*, B. Stoykova[1], P. Petrova[1], N. Gyoshkova[1], G. Ivanova[2], M. Štícha[3], Ts. Milkova[1]

[1] Department of Chemistry, South-West University "Neofit Rilski", 66 Ivan Mihailov Str., 2700 Blagoevgrad (Bulgaria)

[2] REQUIMTE-UCIBIO, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre s/n, 4169-007 Porto (Portugal)

[3] Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, 12843 Prague 2 (Czech Republic)

Received October 10, 2016; Revised January 20, 2017

Cinnamic and hydoxycinnamic acid esters (*α, β*-unsaturated esters), functional derivatives of cinnamic acids (cinnamic, ferulic, sinapic, caffeic) are secondary plant methabolites derived from phenylpropanoid pathway. Cinnamates, of both natural and synthetic origin, continue to elicit great interest due to diversity of biological activities they possess, such as: antioxidant, antimicrobial, anticancer, anti-inflammatory, anti-tyrosinase and etc.

Herein, the reduction of N_{α}- and side chain protected amino acids to *N*-protected amino alcohols and the coupling of the latest with hydroxycinnamic (sinapic and ferulic) acids is described. 1,1-Diphenyl-2-picrylhydrazyl (DPPH$^{\bullet}$) scavenging activities of hydroxycinnamates were compared with their corresponding *N*-hydroxycinnamoyl amino acid amides. Free hydroxycinnamic acids were used as positive controls. The results indicated that *N*-hydroxycinnamoyl amino acid amides exhibited lower scavenging ability than the corresponding free hydroxycinnamic acids, but higher one than hydroxycinnamates.

Keywords: *N*-protected amino alcohols, hydroxycinnamates, *N*-hydroxycinnamoyl amino acid amides, DPPH$^{\bullet}$ scavenging activity

INTRODUCTION

Cinnamic (3-phenyl propenoic) acid and its patterns with different hydroxylated and methoxylated phenyl moiety: *p*-coumaric (4-hydroxycinnamic acid), ferulic (4-hydroxy-3-metoxycinnamic acid), caffeic (3,4-dihydroxycinnamic acid), sinapic (3,5-dimetoxy-4-hydroxy-cinnamic acid)) acids, belong to a diverse group of phenolic compounds. These secondary plant metabolites are biosynthesized via shikimate pathway that is involved in plant adaptation to environmental stress (e. g. microbial pathogens, mechanical wounding, UV irradiation, salinity) [1]. They are found in higher plants predominantly as free cinnamic acids and may occur either in their conjugated forms: *amides* (conjugated with mono- or polyamines, amino acids, or peptides); simple *esters or cinnamates* (derived from corresponding cinnamic acids and alcohol component of quinic acid, shikimic acid, and tartaric acid, and their sugar derivatives) [2]. In particular, chlorogenic acids are the most commonly occurred natural esters of caffeic, ferulic, *p*-coumaric acids with quinic acid [3,4]. Being important biosynthetic polyphenolic intermediates in green coffee, chlorogenic acids are known with numerous bioactive properties, mostly related to their antioxidant activity [5-7].

Besides antioxidant activity, cinnamates have been regarded as photoprotectors, antimicrobials, and effective as anticancer, anti-inflammatory, analgesic, antimicrobial and antithrombotic agents [8-11].

Whereas hydroxycinnamates with alcohols, phenols, saccharides and flavonoids are common phytochemical constituents, those with the participation of the OH group of the side chain of amino acids are very scanty. There are only few reports of such metabolites - caffeic acid esters, derived from insects: *O*-caffeoyltyrosine from *Aonidiella aurantii* (California red scale), *O*-caffeoylserine from *Phenacoccus herreni* (Cassava mealybug) [12, 13] and from plant origin: *L-O*-caffeoylhomoserine [14]. In addition, *O*-caffeoylserine has been also synthetically obtained [15].

The revealed pharmacological activities of hydroxycinnamic acid esters and their small quantities in plants, evoked the interest of organic researchers to design their synthetically analogues.

Ester functionalization of cinnamic acids comprises classical procedures-accomplished via cinnamoylchloride [16], *N,N'*-dicyclohexyl-carbodiimide (DCC) [17] or BOP [18] as coupling agents. Moreover, those compounds can also be obtained using Wittig reaction under different

* To whom all correspondence should be sent:
E-mail: mayabg2002@yahoo.com

conditions [19-22] and as well as green esterification procedures [23-27].

Considering the importance of phenolic compounds, e.g. hydroxycinnamic acid esters for removal of oxidative stress, and thus to prevent lifestyle-related diseases such as cancer, diabetes or heart diseases, herein we prepared hydroxycinnamic acid esters and tested them as scavengers against DPPH radical.

EXPERIMENTAL

General information

All amino acid derivatives, ferulic (3-methoxy-4-hydroxy-cinnamic, **FA**), sinapic (3,5-dimethoxy-4-hydroxy-cinnamic, **SA**) acids, as well as isobutyl chloroformate (IBCF), 4-methylmorpholine (NMM), 4-(dimethylamino)pyridine (DMAP), dicyclohexylcarbodiimide (DCC), $NaBH_4$, 1,1-diphenyl-2-picrylhydrazyl radical (DPPH$^{\bullet}$) were purchased from Sigma Aldrich (FOT, Bulgaria). Tetrahydrofuran was obtained from Fisher Chemical (Bulgaria) and further was distilled over $LiAlH_4$ and stored under argon. All other solvents were of reagent grade and used without further purification.

Thin-layer chromatography (TLC) was conducted on precoated Kieselgel 60F254 plates (Merck, Germany). Separation of the compounds by preparative thin layer chromatography with silica gel 60 GF254 (Merck, Bulgaria).

The NMR experiments were recorded on Bruker Avance III 600 or Bruker Avance III 400 spectrometer, operating at 600.13 and 400.15 MHz for protons respectively. The measurements in $CDCl_3$ solutions were carried out at ambient temperature (300 K) and tetramethylsilane (TMS) was used as an internal standard. The UV spectra of the compounds were measured with an ''Agilent 8453'' UV-vis spectrophotometer. Electrospray Ionisation (ESI) and EI mass spectra were recorded corresponding on an Esquire 3000 and MAT 8230. Attenuated total reflectance infrared spectroscopy (ATR-IR) measurements were performed using Thermo Scientific Nicolet iS10 FT-IR device with ID5 ATR accessory (diamond crystal).

N-protected amino acids (Boc-Cys(Bzl)-OH (**1a**) and Boc-Val-OH (**1b**) were converted into corresponding alcohols Boc-Cys(Bzl)-ol (**2a**) and Boc-Val-ol (**2b**), following a modified procedure developed by Kokotos [28] (Scheme 1).

General procedures

Synthesis of 2a, b (a modified method reported by Kokotos [28]. A solution of 1.6 mmol *N*-protected amino acid (**1a, b)** in 10 ml dry THF is cooled to −15°C and added 0.18 ml (1.6 mmol) *N*-methylmorpholine. Isobutyl chloroformate (0.24 ml, 1.7 mmol) is added dropwise to make sure that the internal temperature does not rise above -10 °C. About 5-8 minutes later, to the white suspension of formed isobutylcarbonic acid mixed anhydrides[29] is added 0.104 g (2.74 mmol) $NaBH_4$ in 10 ml THF, and for a period of 10 min abs.CH_3OH (5 ml) is added dropwise. Stirring is continued and the progress of the reaction is monitored by thin layer chromatograms (hexane:ethylacetate=1:1).

At the completion of the reduction (2h) the solvent is evaporated under reduced pressure. The residue is dissolved in ethylacetate and is washed twice consequently with 5% $NaHSO_4$, 5% $NaHCO_3$ and finally with saturated sodium chloride solution. The organic phase is dried over Na_2SO_4, filtered and the solvent removed *in vacuo.* The obtained crude product is purified by preparative thin layer chromatography (hexane:ethylacetate= 3:1).

S-Benzyl-*N*-(*tert*-butoxycarbonyl)-*L*-cysteinol ***(Boc-Cys(Bzl)-ol) (2a)*** white crystal, 61% yield; **ESI-MS:** 617.1 $[2M+Na]^+$, 595.1 $[2M+H]^+$, 336.3 $[M+K]^+$, 320.1 $[M+Na]^+$, 298.2 $[M+H]^+$; **IR (ATR)u_{max}:** 3342.65, 1679.47, 1527.03, 1340.92, 1311.44, 1284.20, 1164.34, 1004.33, 698.47 cm^{-1};

N-(*tert*-butoxycarbonyl)-*L*-valinol ***(Boc-Val-ol) (2b)*** *yellow* oil, 53% yield;

^{1}H NMR ($CDCl_3$, δ ppm): 0.9 (dd, 6H, -CH(C**H$_3$)$_2$**), 1.2 (s, 9H, -C(C**H$_3$)$_3$**), 1.8-1.84 (m, 1H, -C**H**$(CH_3)_2$), 3.4-3.6 (m, 3H, -C**H**$_2$OH, -NH-C**H**<), 4.8 (br. s, 1H, NH); **EI-MS:** 57.1, 73, 116.1, 130, 172.1, 203 $[M^+]$; **IR (ATR)u_{max}**:3318.1, 3189.5, 2978.6, 1679.7, 1366.5, 1289.4, 1150.7, 1011.8, 908.9, 772.0, 699.4

Esterification of cinnamic acids with N-protected amino alcohol [30]. Cinnamic acids (1.5 mmol), DCC (1.5 mmol) and DMAP (0.0224 mmol) are dissolved in 10 mL of dry THF. The reaction mixture is stirred under argon at 0°C and then, after 10 min *N*-protected amino alcohol (0.6 mmol) is added. The mixture is kept under vigorous stirring and cooling (0°C) for 60 min and then is allowed to stand at room temperature overnight. The residue of dicyclohexylcarbamide is filtered and washed with cold ethylacetate. The combined solutions are evaporated under vacuum and the residue is purified by column chromatography on silica.

Ferulate of Boc-Val-ol, 35% yield. **UV** (C_2H_5OH) λ max = 203, 218, 236, 328 nm; **IR (ATR)u_{max}:** 3335.5, 2959.6, 2932.1, 1707.2, 1627.4, 1592.3, 1510.9, 1365.5, 1269.7, 1246.7, 1157.4, 1119.8, 1029.32, 978.9 cm^{-1}; **^{1}H NMR** ($CDCl_3$) /600 MHz/ δ = 0.9 (dd, 6H, -CH(C**H$_3$)$_2$**), 1.2 (s, 9H, -C(C**H$_3$)$_3$**), 1.8 (m, 1H, -C**H**$(CH_3)_2$), 3.7 (s, 2H, -OC**H$_2$**-), 3.8 (s, 3H, -OC**H$_3$**), 4.1 (m, 1H, -NH-C**H**<), 5.0 (br. s, 1H, N**H**), 6.2 (d, 1H, J=15.5 Hz, -CH=C**H**-

), 7.00-7.03 (m, 3H, Ar-**H**), 7.5 (d, 1H, J=15.5 Hz, -C**H**=CH-); **ESI-MS:** 380.2 $[M+H]^+$, 409.12 $[M+Na]^+$

***Sinapate of Boc-Val-ol*, 49 % yield**. **UV** (C_2H_5OH) λ max = 203,229, 329 nm; **IR (ATR)u_{max}:** 3376.3, 2936.4, 2844.2, 1704.6, 1632.7, 1594.5, 1456.2, 1419.11, 1338.1, 1275.2, 1204.2, 1111.6, 980.1, 822.8 cm^{-1}; **^{1}H-NMR** ($CDCl_3$) /600 MHz/ δ = 0.9 (dd, 6H, -CH(C**H_3)$_2$**), 1.2 (s, 9H, -C(C**H_3)$_3$**), 1.8 (m, 1H, -C**H**$(CH_3)_2$), 3.7 (s, 2H, -OC**H_2**-), 3.8 (s, 6H, 2 x-OC**H_3**), 4.2 (m, 1H, NH-C**H**), 5.6 (br. s, 1H, N**H**), 6.5 (d, 1H, J = 15.5 Hz, -C**H**=CH-), 6.7 (s, 2H, Ar-**H**), 7.5 (d, 1H, J = 15.5 Hz, -CH=C**H**-); **EI-MS:** 57.1, 207.1, 308, 238.1, 336.2, 353.2, 409.2 $[M^+]$.

***Ferulate of Boc-Cys(Bzl)-ol*, 20 % yield**. **UV** (C_2H_5OH) λ max = 203,217, 236, 327 nm; **IR (ATR)umax:** 3343.4, 1679.7, 1526.6, 1364.7, 1340.9, 1311.3, 1284.1, 1163.2, 1076.9, 1003.9, 698.6 cm^{-1}; **^{1}H NMR** (DMSO-d_6, ppm): δ 1.42 (s, 9H, -C(C**H_3**)$_3$), 3.21 (dd, J=14.2, 5.2 Hz, 1H, CHC**H_{2a}**), 3.4 (dd, J=14.2, 4.6 Hz, 1H, CHC**H_{2b}**), 3.66 (d, J=5.6 Hz, 2H, -S-C**H_2**-Ph), 3.73 (s, 3H, OC**H_3**), 4.42 (d, 2H, -CH_2-O -), 4.87 (ddd, J= 7.0, 5.2, 4.6 Hz, 1H, C**H**CH2), 5.82 (br. s, 1H, O**H**), 6.28 (d, J=7.0 Hz, 1H, N**H**), 6.32 (d, J=15.6 Hz, 1H,-CH=C**H**-), 6.93 (d, J=8.0 Hz, 1H, m-Ar**H**), 7.01 (d, J=1.6 Hz, 1H, o-Ar**H**),7.06 (dd, J=8.0, 1.6 Hz, 1H, o-Ar**H**), 7.24 (m, 5H, Ar-**H**), 7.57 (d, J=15.6 Hz, 1H, -C**H**=CH-); **EI-MS:** 57.1, 91.0, 177.1, 473.3 $[M^+]$

Sinapate of Boc-Cys(Bzl)-ol, yield 25 *%*

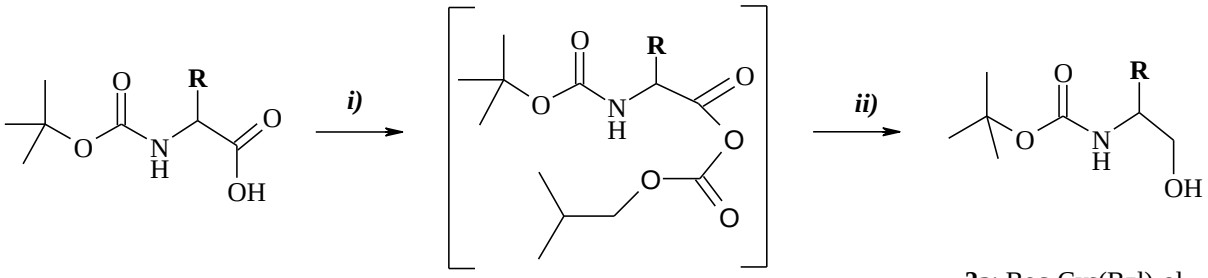
UV (C_2H_5OH) λ max = 203,228, 330 nm; **IR (ATR)umax**: 3392.8, 1705.1, 1597.5, 1507.1, 1456.8, 1418.8, 1108.3, 870.4, 659.0 cm^{-1}; **^{1}H NMR** (DMSO-d_6, ppm): δ 1.42 (s, 9H, -C(**CH_3**)$_3$), 3.71 (dd, J=14.2, 5.2 Hz, 1H, CHC**H_{2a}**), 3.4 (dd, J=14.2, 4.6 Hz, 1H, CHC**H_{2b}**), 3.68 (d, J=5.6 Hz, 2H, -S-C**H_2**-Ph), 3.73 (s, 6H, 2x OC**H_3**), 4.51 (d, 2H, -C**H_2**-O-), 4.63 (ddd, J= 7.0, 5.2, 4.6 Hz, 1H, C**H**CH2), 5.72 (s, 1H, O**H**), 6.28 (d, J=7.0 Hz, 1H, N**H**), 6.32 (d, J=15.6 Hz, 1H, =C**H**), 6.7 (s, 2H, Ar-H), 7.28-7.51 (m, 5H, Ar-H), 7.59 (d, J=15.6 Hz, 1H, =C**H**); **EI-MS:** 57.1, 91.0, 207.1, 238.1, 266.1, 386.3, 447.1, 503.3 $[M^+]$.

RESULTS AND DISCUSSION

Herein, in order to elucidate the antiradical activity of cinnamic acid esters, we firstly obtained synthetically the amino alcohols (used as intermediates).

By applying a modified method [28], the $NaBH_4$ reduction of protected amino acids (Scheme1; **1a,b**) into corresponding amino alcohols (**2a, b**) was occurred by means of *in situ* formed isobutylcarbonic acid mixed anhydrides in THF. However, the establishment that the reducing power of $NaBH_4$ in THF increases when methanol is added drop-wise [28] enforces us to accomplish the reaction in the same manner. The expected amino alcohols were isolated on silica gel by preparative thin layer chromatography (hexane:ethylacetate) in moderate yields.

The hydroxycinnamic acid esters (**Table 1**, **3a-d**) were prepared by esterification of sinapic- (SA) and ferulic (FA) acids with compounds **2a, b** using DCC/DMAP method [30]. The structures of desired hydroxycinnamates were elucidated by UV, IR, ESI(EI)-MS and ^{1}H-NMR spectroscopic analyses.

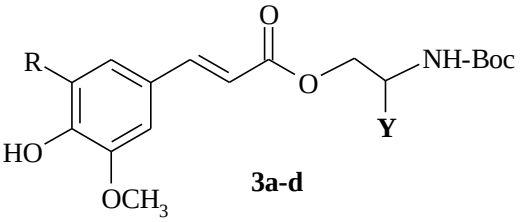
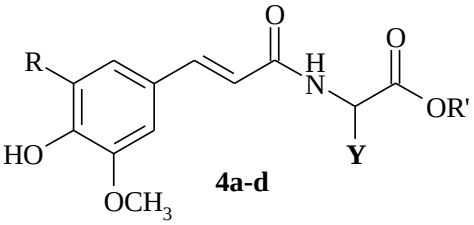


1a: Boc-Cys(Bzl)-OH; R=CH_2-S-CH_2-C_6H_5
1b: Boc-Val-OH; R=$CH(CH_3)_2$

2a: Boc-Cys(Bzl)-ol
2b: Boc-Val-ol

Scheme 1. i) IBCF/NMM, THF, -15˚C **ii)** $NaBH_4$, CH_3OH

Table. 1. Structures of hydroxycinnamic derivatives studied and their DPPH•-scavenging activity.

Compounds	RSA %			
	R	R'	Y	3.6 mM 20'
 **3a-d**				
FA ester of BocCys(Bzl)ol (**3a**)	H	-	$-CH_2$-S-Bzl	27.0±0.1
SA ester of BocCys(Bzl)ol (**3b**)	OCH_3	-	$-CH_2$-S-Bzl	29.9±0.2
FA ester of BocVal-ol (**3c**)	H	-	$-CH(CH_3)_2$	17.6±0.2
SA ester of BocVal-ol (**3d**)	OCH_3	-	$-CH(CH_3)_2$	19.7±0.1
 **4a-d**				
FA-Cys(Bzl)-OEt* (**4a**)	H	C_2H_5	$-CH_2$-S-Bzl	38.4±1.2
SA-Cys(Bzl)-OEt*(**4b**)	OCH_3	C_2H_5	$-CH_2$-S-Bzl	47.4±2.4
FA-Val-OCH_3 (**4c**)	H	CH_3	$-CH(CH_3)_2$	30.8±0.2
SA-Val-OCH_3 (**4d**)	OCH_3	CH_3	$-CH(CH_3)_2$	35.1±0.1
Sinapic acid (SA)		-	-	68.0±0.3
Ferulic acid (FA)		-	-	45.2±0.1

% RSA—percent radical scavenging activity; % RSA = [$Abs_{516nm\ (t\ =\ 0)}$ - $Abs_{516nm(t\ =\ t'\ )}$ x 100/$Abs_{516nm(t\ =\ 0)}$]; sinapic-and ferulic acids were used as standards.

*The RSA of hydroxycinnamoylamides were previously reported [32] and were used for comparison.

The values of the proton-proton vicinal coupling constants ($^3J_{H/H}$ about 15.5 Hz) measured for the olefinic protons of feruloyl- and sinapoyl moieties define *E* configuration of the double bond of the studied compounds (**3a-d**).

Highlighting the valuble role of hydroxycinnamic acid derivatives as antioxidants, the search for new, more effective and better radical scavengers is a major challenge.

1,1-Diphenyl-2-picrylhydrazyl radical (DPPH·) scavenging activity

Being stable and commercially available organic nitrogen radical, DPPH• is often used for primary assessment of antioxidant activity. DPPH method gives rapid and highly reproducible results, therefore we applied this method to estimate and compared the radical scavenging abilities of the synthesized hydroxycinnamic acid derivatives (esters and amides).

As shown in Table 1, % RSA values of hydroxycinnamic acid (sinapic and ferulic) and their derivatives are presented for 20-min reaction period (3.6 mM), as proposed by Nenadis et al. [31].

The DPPH scavenging activity of hydroxycinnamates (**3a-d**) was compared with those of corresponding previously synthesized amides (**4a-d**). Results obtained indicated that amide derivatives (**4a-d**) were found to be more potent than corresponding hydroxycinnamic esters (**3a-d**). The established increase of antiradical activity in hydroxycinnamoyl amino acid amides may be due to the presence of other hydrogen-donating amide group. By comparison of DPPH activity of studied esters and amides with their corresponding free cinnamic acids the higher radical scavenging ability of the parent acids was established. Actually, *N*-sinapoyl amide of cysteine (SA-Cys(Bzl)-OEt (**4b**)) showed similar DPPH scavenging activity as ferulic acid was [32]. Moreover, our results are in a good correlation with those presented elsewhere, that

introduction of additional methoxyl group in an *ortho*-position to a hydroxyl group (such as in sinapic acid series, Table_1) is an important for the radical scavenging activities of phenolic acids.

CONCLUSION

In our study *N*-protected amino alcohols were chemically obtained and further used as intermediate analogues for synthesis of hydroxycinnamates.

The sinnapic and ferulic acid derivatives (esters and amides) were tested and compared for their *in vitro* antiradical activity towards DPPH radical. It was found that *N*-hydroxycinnamoyl amino acid amides showed better radical scavenging activity than the corresponding hydroxycinnamates, whereas the free hydroxycinnamic acids (used as standards) remained the most active ones in this test.

Acknowledgements: *The authors gratefully acknowledge financial support from South-West University "Neofit Rilski" – grant RP-A9/16.*

REFERENCES

1. K. M. Hermann, *Plant Physiol.*, **107**, 7 (1995).
2. K. Herrmann, *CRC Crit. Rev. Food Sci. Nutr.*, **28**, 315 (1989).
3 M. N. Clifford, *J. Sci. Food Agric*., **79**, 362 (1999).
4. M. N. Clifford, *J. Sci. Food Agric*., **80**, 1033 (2000).
5. C. A. Rice-Evans, N. J. Miller, G. Paganga, *Trends Plant Sci.*, **2**, 152 (1997).
6. H. Kasai, S. Fukada, Z. Yamaizumi, S. Sugie, H. Mori, *Food Chem. Toxicol*., **38**, 467 (2000).
7. T. Tanaka, T. Kojima, T. Kawamori, A. Wang, M. Suzui, K. Okamoto, H. Mori, *Carcinogenesis*, **14**, 1321 (1993).
8. M. Sova, *Mini-Rev. Med. Chem.* **12**, 749 (2012).
9. S. Son, B.A. Lewis, *J. Agric. Food. Chem.*, **50**, 468 (2002).
10. A. Ivanova, Ts. Milkova, A. S. Galabov, L. Nikolaeva, E. Voynova, *Z. Naturforsch.*, **52c**, 516 (1997).
11. M. D. Santos, M. C. Almeida, N. P. Lopes, G.E.P. Souza, *Biol Pharm Bull*., **29**, 2236 (2006).
12. J.G. Miller, J.D. Hare, *J. Chem. Ecol.*, **19**, 1721 (1993).
13. P.A. Calatayud, J. Auger, E. Thibout, S. Rousset, A.M., Caicedo, S. Calatayud, H Buschmann, J. Guillaud, M. Mandon, A.C. Bellotti, *J. Chem. Ecol.*, **27**, 2203 (2001).
14. T. Kimura, M. Suzuki, M. Takenaka, K. Yamagishi, H. Shinmoto, *Phytochemistry*, **65**, 423 (2004).
15. Z. Lin, M. Neamati, H. Zhao, Y. Kiryu, J.A. Tuppin, C. Aberham, K. Strebel, K. Kohn, M Witvrouw., C. Pannecouque, Z. Debyser, E. De Clercq, W.G. Rice, Y. Pommier, T. R. Burke, *J. Med. Chem.*, **42**, 1401 (1999).
16. E. Womack, J. McWhirter, *Org. Synth. Coll*., **3**, 714 (1955).
17. N. Isaacs, T. Najem, *J. Chem. Soc. Perkin Trans.*, **2**, 557 (1988).
18. S. Gobec, M. Sova, K. Kristan, T. L. Rizner, *Bioorg*. *Med. Chem. Lett.*, **14**, 3933 (2004).
19. R. Mali, A. Papalkar, *J. Chem. Res.* (S) **10**, 603 (2003).
20. I. Elenkov, D. Todorova, V. Bankova, Ts. Milkova, *J. Nat. Prod*., **58**, 280 **(**1995).
21. M. Spasova, V. Bankova, G. Ivanova, T. Pajpanova, Ts. Milkova, *Oxid.Commun*., **29**, 172 (2006).
22. J. Westman, *Org. Lett.*, **3**, 3745 (2001).
23. D. M. Ruiz, G. P. Romanelli, D. O. Bennardi,. G. T. Baronetti,. H. J. Thomas, J. C. Autinoa, *Arkivoc*, **12**, 269 (2008).
24. V. Palermo, D. Ruiz, J. Autino, P. Vázquez, G. Romanelli, *Pure Appl. Chem*., **84**, 529 (2012).
25. M. Nakayama, A Sato, K. Ishihara, H. Yamamoto, *Adv. Synth. Catal*., **346**, 1275 (2004).
26. A. Sinha, A. Sharma, A. Swaroop, V. Kumar, *Tetrahedron*, 63, 1000 (2007).
27. G. Romanelli, D. Ruiz, P. Vázquez, H. Thomas, J. Autino, *Chem. Eng. J.*, **161**, 355 (2010).
28. G. Kokotos, *Synthesis*, **1990**, 299 (1990).
29. J. R Vaughan, R. L. Jr., Osato, *J. Amer. Chern. Soc*., **73**, 3547 (1951).
30. B. Neises, W. Steglich, Angew. Chem., *Int. Ed. Engl.*, **17**, 522 (1978).
31. N. Nenadis, M. Tsimidou, *JAOCS*, **79**, 1191 (2002).
32. M. G. Chochkova, E. Y. Chorbadzhiyska, G. I. Ivanova, H. Najdenski, M. Ninova, Ts. S. Milkova, *Nat. Prod. J.*, **2**, 50 (2012).

СИНТЕЗ И ИЗСЛЕДВАНЕ НА РАДИКАЛ-УЛАВЯЩА АКТИВНОСТ НА ЕСТЕРИ НА КАНЕЛЕНИТЕ КИСЕЛИНИ

М. Чочкова[1]*, Б. Стойкова[1], П. Петрова[1], Н. Гьошкова[1], Г. Иванова[2], М. Щиха[3], Ц. Милкова[1]

[1]Катедра по химия, Югозападен университет „Неофит Рилски“, ул. „Иван Михайлов“ № 66, 2700 Благоевград (България)

[2]Департамент по химия и биохимия, Университет в Порто, ул. Кампо Алегре с/н, 4169-007 Порто (Португалия)

[3] Департамент по органична химия, Карлов университет, Хлавова 2030/8, 12843 Прага 2 (Чехия)

Постъпила на 10 октомври, 2016 г.; Коригирана на 20 януари, 2017 г.

(Резюме)

Канелената, хидроксиканелените киселини (ферулова, синапова, кафеена) и техните естери представляват вторични растителни метаболити, биосинтезирани от фенилпропаноидния метаболитен път. Природните хидроксицинамати и техните синтетични аналози привличат вниманието на изследователите поради широкия спектър от биологични активности като: антиоксидантна, антимикробиална, противотуморна, противовъзпалителна, тирозиназно-инхибиторна и др.

В настоящето изследване е разгледана редукция на карбоксилната група на защитени аминокарбоксилни киселини на N_α -място и в страничната верига. След естерифициране на получените аминоалкохоли с хидроксиканелени (синапова и ферулова) киселини, новосинтезираните производни са подложени на изследване за радикалулавяща активност спрямо 1,1-Дифенил-2-пикрилхидразилов радикал (DPPH$^\bullet$). Резултатите от антирадикаловата активност на хидроксицинаматите са сравнени с тези на съответните хидроксицинамоиламиди с аминокарбоксилни киселини. Като стандартни антиоксиданти са използвани свободните хидроксиканелени киселини. Установено е, че хидроксицинамоиламидите показват по-ниска антирадикалова активност от съответните свободни хидроксиканелени киселини, но по-висока от тази на хидроксицинаматите.