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Synthesis and antimicrobial activity of novel kojyl carbamates

B. Stoykova[1], M. Chochkova[1*], I. Tsvetkova[2], H. Najdenski[2], M. Štícha[3], K. Ranchova[1], Ts. Milkova[1]

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

[2] *The Stephan Angeloff Institute of Microbiology Bulgarian Academy of Sciences, 26 Georgi Bonchev Str., 1113 Sofia, Bulgaria*

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

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Novel kojyl carbamates of amantadine, rimantadine and oseltamivir were synthesized and assayed to evaluate their antimicrobial activity. The newly compounds were prepared by using EDC/HOBt method at preliminary activation of kojic acid. The structures of the synthesized kojyl derivatives were confirmed by mp, UV, IR (ATR)u_{max}, ESI-MS. According to the antimicrobial activity studies performed *in vitro*, kojyl carbamate of rimantadine (4) displayed the highest antibacterial activity (MIC: 31 μg/mL) against two Gram-positive (*Staphylococcus aureus, Bacillus subtilis*) bacteria. Moreover, this compound (4) showed about 4-fold better activity against two Gram-negative bacteria tested (*Escherichia coli, Pseudomonas aeruginosa*). Amongst the examined kojyl carbamates, the rimantadine derivative of kojic acid (4) exhibited the highest antifungal activity (*Candida albicans*) as well.

Keywords: kojic acid, kojyl carbamates, antibacterial activity, antifungal activity

INTRODUCTION

In the recent years, unsafe food poses serious health problems, endangering people worldwide [1]. The WHO report reveals that food-borne illnesses are usually caused by pathogens (bacteria, parasites, viruses) or by harmful substances entering the body through contaminated food or water. Particularly, vulnerable to those threats are infants, young children, pregnant women, and elderly persons. It is estimated that food intoxications by harmful pathogens and/or their toxins or chemicals, cause more than 200 diseases – ranging from diarrhoea to cancers [1].

Indeed, food-borne diseases impede not only the health-care systems, but also economics, and tourism. Therefore, many screening efforts have been spent to find new antimicrobial agents of natural or synthetic origin that can specifically act on different molecular targets to control infections caused by various microorganisms [2-6].

Kojic acid, 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one (1, KA) is a naturally occurring scaffold of biological importance. It is well known that this secondary metabolite is produced *via* diverse carbohydrate sources in an aerobic condition by fungal or bacterial strains, such as *Aspergillus oryzae*, *Penicillium* or *Acetobacter spp*. Amongst them, *A. flavus* [7,8], *A. oryzae* [9,10], *A. tamarii* [11] and *A. parasiticus* [12-14] have been reported. KA also emerges as a common by-product in the fermentation of soy sauce, sake and rice wine [15-17].

As most of the secondary metabolites, kojic acid has been found to possess a multitude of biological activities with a wide range of applications in various industries, such as: pharmaceutical and medicine - for the treatment of chloasma, as anti-diabetic and antitumor agent [15, 16, 23]; in the cosmetic field - as whitening, radioprotective, skin anti-aging agent; in agriculture - as pesticide or insecticide[24-28] [29], or as plant growth regulating agent to increase production, and others.

Additionally, kojic acid has the antibiotic potential to affect human tubercle bacilli, Gram-positive and Gram-negative microorganisms *in vitro*. Also, its derivatives such as azidometalkojates are known to act as antifungal and antibacterial agents on several genera like *Bacillus Staphylococcus, Saccharomyces, Aspergillus, Rhizopus*, and *Fusarium* [30].

Currently, there were only few reports concerning the antimicrobial properties of kojic acid against food-borne pathogenic bacteria.

Wu *et al.* found that KA exhibited significant activity against Gram-positive bacteria (*Listeria*

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

monocytogenes, Bacillus subtilis, and Staphylococcus aureus) and Gram-negative ones (*Escherichia coli and Salmonella typhimurium*).

They found that Gram-negative bacteria are more susceptible to KA than Gram-positive ones [31]. Moreover, notable antifungal activity against *Candida albicans* and *Candida krusei* was found for kojic acid carboxamides with various substituents [16, 32-34].

Aytemir and Özçelik showed that the chlorokojic acid-bearing Mannich base derivatives were highly active (MIC: 1-2 μg/mL) against sykrani *B. subtilis* and *S. aureus*, whereas some of them showed significant activity against *E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Acinetobacter baumannii*. The compounds were also found to be remarkably active against *C. albicans* and *Candida parapsilosis* (MIC: 4-8 μg/mL). However, contrary to the established activity, only one of derivatives was active against human parainfluenza virus type 3 [35].

On the other hand, some data also revealed KA as a potential chemo sensitizer. Its combination with commercial antimicrobial agents has been found to evoke better effect than the monotherapy [36, 37].

Adamantane analogues emerge as another group of compounds that are considered as invaluable chemotherapeutics. The adamantane nucleus could substantially affect lipophilicity, pharmacological properties and biological activity of the parent molecule. Hence, adamantane could positively modulate the therapeutic index of the parent molecule and has been widely used in designing of agents with potential antimicrobial activity [38].

Over the last few years synthesis of novel hybrid molecules with improved biological efficacy has made remarkable progress in medicinal chemistry research. Tailoring the available prodrugs with heterocycle moiety represents a valuable tool to obtain novel compounds with enhanced biological activity [39, 40].

Considering the potential impact of the hydrophobicity of the adamantane moiety and kojic acid residue as crucial factor for the antimicrobial activity, herein we report the synthesis and *in vitro* antibacterial and antifungal activities of unique hybrid molecules by combining of these two fragments.

EXPERIMENTAL

General information

All chemicals used in this study were purchased from Sigma-Aldrich (FOT, Bulgaria). Synthesized compounds were purified by column chromatography using silica gel (Acros Organics, mesh 35-70) and identified by TLC, UV, IR, NMR, and MS analysis. TLC was carried out on silica gel $60F_{254}$ (Merck) precoated aluminium plates. Melting points were determined using Stuart SMP10 apparatus and are uncorrected. The UV spectra of the compounds were measured by Agilent 8453 UV-vis spectrophotometer. Attenuated total reflectance infrared spectroscopy (ATR-IR) measurements were performed by Thermo Scientific Nicolet iS10 FT-IR device with ID5 ATR accessory (diamond crystal). ^{1}H-NMR spectra were recorded on a Bruker BioSpin GmbH (Prague) 600 MHz spectrometer in dimethyl sulfoxide-d_6 (DMSO-d_6) solution. The ESI mass spectra were recorded on Esquire 3000 plus instrument.

*Synthesis of kojic acid-7-imidazolide (compound **2**)* [41]

Kojic acid (1 g, 7 mmol) was dissolved in a mixture of 10 ml of THF (dry) and 1 ml of DMF in argon atmosphere. After 1 h of stirring CDI (1.02 g, 6.3 mmol) was added. The completion of the reaction (24 h) was monitored by TLC (PE/ EtOAc = 1.0:1.8). The formed white crystals (compound **1**) were filtered, washed with cold THF and dried *in vacuo*.

Yield: 63%; mp ~ 145-149°C; UV (C_2H_5OH) λ_{max} = 214, 273 nm; IR (ATR)u_{max}: 3410, 3093, 2944, 1743, 1448 cm^{-1}; 600 MHz ^{1}H-NMR (DMSO-d_6, ppm): δ 4.75 (s, 2H, -C<u>H</u>$_2$-O-), 6.59 (s, 1H, >C<u>H</u>-C(O)-), 7.15 (s, 1H, imidazole), 7.56 (s, 1H, imidazole), 8.06 (s, 1H, >C<u>H</u>-O-), 8.25 (s, 1H, imidazole), 9.31 (s, 1H, -O<u>H</u>).

*General procedure for synthesis of kojyl carbamates (**3-5**)*

The urethane bond formation in the desired compounds (**3-5**) was carried out under modified conditions by means of the peptide coupling method EDC/HOBt [42].

Activated kojic acid derivative (**2**) (0.150 g, 0.64 mmol) was dissolved in 6 ml of a CH_2Cl_2/DMF (5/1) mixture and cooled to 0°C in argon atmosphere. Then, HOBt (0.086 g, 0.64 mmol) and EDC (0.121 g, 0.64 mmol) were added to the cooled solution. After 5-8 min, the corresponding anti-influenza agent (0.64 mmol) in 2 ml of CH_2Cl_2 along with 0.07 ml (0.64 mmol) of NMM were added to the formed mixture. The reaction mixture was left overnight under stirring at room temperature. After completion of the

reaction, controlled by TLC ($CHCl_3$:CH_3OH = 2.0:1.0; 2.5:0.5), the solvents were evaporated *in vacuo*. Then, the residue was dissolved in EtOAc and washed subsequently with 5% $NaHCO_3$ (× 3) and distilled water (× 3). The crude product was subjected to preparative chromatography to afford the desired kojyl carbamates. The physico-chemical parameters and the IR, MS spectral data of the compounds **3-5** are as follows:

*Kojyl carbamate of amantadine (**3**):* Yield: 14 %; mp ~ 170-174°C; UV (C_2H_5OH) λ_{max} = 213, 267 nm; IR (ATR)u_{max}: 3324, 3170, 3102, 2979, 2991, 2906, 2850, 1695, 1650, 1633, 1545, 1446, 1245, 1204 cm^{-1}; ESI-MS: 320.2 $[M+H]^+$, 343.4 $[M+Na]^+$.

*Kojyl carbamate of rimantadine (**4**):*Yield: 17 %; mp ~ 170-172°C; UV (C_2H_5OH) λ_{max} = 203, 217, 271 nm; IR (ATR)u_{max}: 3326, 3172, 3107, 2977, 2989, 2907, 2848, 1690, 1652, 1629, 1547, 1445, 1381, 1246, 1205 cm^{-1}; ESI-MS: 348.2 $[M+H]^+$, 370.2 $[M+Na]^+$.

*Kojyl carbamate of oseltamivir (**5**):* Yield: 25 %; mp ~ 178-182°C; UV (C_2H_5OH) λ_{max} = 214, 270 nm; IR (ATR)u_{max}: 3277, 3094, 2965, 2935, 2877, 1716, 1652, 1622, 1539, 1455, 1251, 1167, 1047, 733 cm^{-1}; ESI-MS: 479.1 $[M-H]^-$, 481.2 $[M+H]^+$, 503.2 $[M+Na]^+$, 515.1 $[M+Cl]^-$.

Microbiology

The antibacterial activity was tested against *S. aureus 209*, *B. subtilis 1A95* (Gram-positive bacteria) and *P. aeruginosa 5749*, *E. coli WF+* (Gram-negative bacteria), whereas the antifungal activity was tested against the pathogenic fungus *C. albicans 5*62. All microorganisms were obtained from the Bulgarian National Collection for Microorganisms and Cell Cultures (NBIMCC).

The minimal inhibitory concentrations (MICs) of all samples were determined by the microdilution method described by Andrews [43]. MIC is defined as the lowest concentration of the examined sample that inhibits the visible microbial growth after 24 h incubation at 37°C. For positive controls commercially available antibiotics tobramycin and ketoconazole were used. The solvent DMSO was tested as negative control. Three replicates were done for each compound.

RESULTS AND DISCUSSION

Chemistry

It is noteworthy that kojic acid, being a natural occurring multi-functional skeleton, is an attractive molecule for development of numerous biologically active compounds by its chemical transformations [44].

This enforced us to connect its molecule with anti-influenza drugs (amantadine (Am), rimantadine (Rim) and oseltamivir (Os)) *via* a carbamate linker. This functionality is an object of our interest due to its participation as key structural moiety in various approved therapeutic agents [34]. In this context, for urethane linking of kojic acid (**1**) with the amino group of anti-influenza drugs (amantadine, rimantadine and oseltamivir) it was necessary the C-2 hydroxyl group of kojic acid to be previously transformed. The activation step of its molecule was accomplished following Scheme 1 (*stage **i***), using a method described in the literature [41].

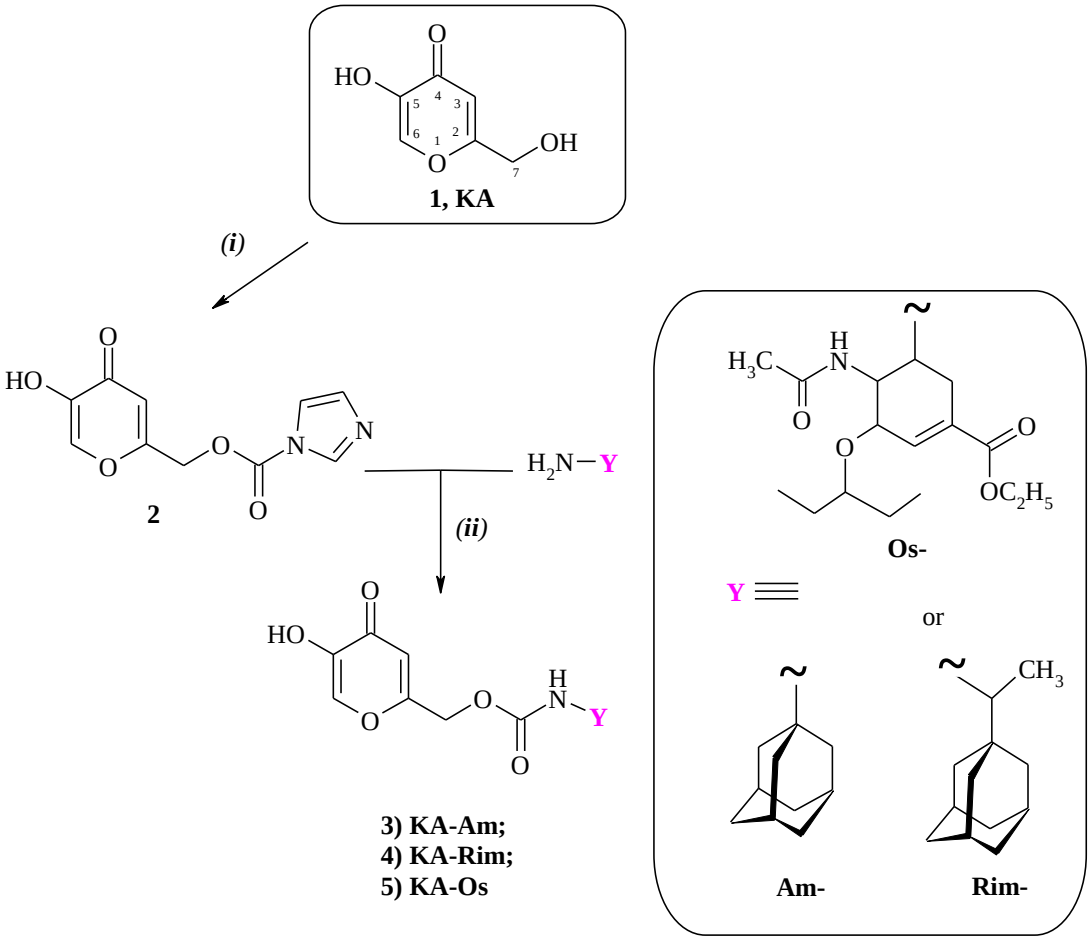
The activated kojic acid (**2,** kojic acid-7-imidazolide) was formed by carbonyldiimidazole (CDI) without selective protection of the hydroxyl group at position C-5. In order to increase kojic acid solubility in tetrahydrofuran (THF), a small amount of dimethylformamide (DMF) was added. However, to avoid the side oxidation reaction of the kojyl moiety, the reaction was accomplished at room temperature in argon atmosphere. The kojic acid-7-imidazolide (**2)** was obtained as white crystals in a sufficient yield of 63 %.

In the next step (*ii*), following Scheme 1, the preliminarily obtained kojic acid-7-imidazolide (**2**) was subjected to EDC/HOBt coupling with the amino group of anti-influenza drugs, which afforded kojyl-carbamates (**3-5**). The desired kojic derivatives **3–5** were isolated on silica gel by preparative TLC plates with fluorescence indicator (Merck). The structures of the new carbamates were confirmed by mp, UV, IR (ATR)u_{max}, ESI-MS.

Evaluation of antimicrobial activity in vitro

The antimicrobial activities of all compounds were screened *in vitro* against four bacterial species - two of them were Gram-positive (*S. aureus 209*, *B. subtilis 1A95*), the other were Gram-negative (*P. aeruginosa 5749*, *E. coli WF+*); as well as against the pathogenic fungus *C. albicans 5*62.

Tobramycin and ketoconazole were used as positive controls for comparison in antibacterial and antifungal assays, respectively. MICs of the tested compounds are described in Table 1.



Scheme 1. Synthetic route of kojic derivatives. Reagents and conditions: (***i***) 1,1'-carbonyldiimidazole (CDI), dry THF/ DMF (***ii***) EDC/HOBt, NMM in CH_2Cl_2/ DMF

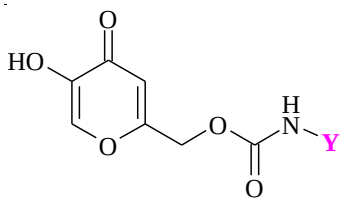
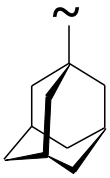
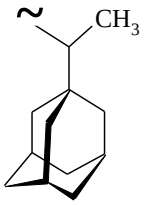
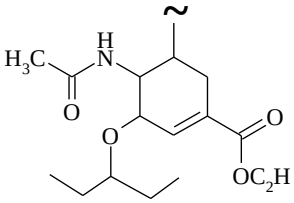
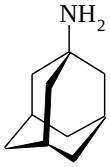
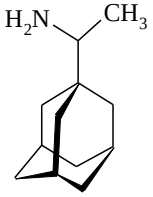
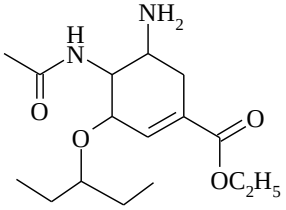
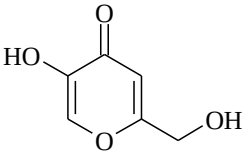
Taking into consideration the antimicrobial effects of the individual parent molecules (kojic acid, amantadine, rimantadine, oseltamivir), herein, to assess the impact of carbamate linkage on the activity, the covalently obtained kojyl hybrids (compounds, **3-5**) along with the parents were investigated. As shown in Table 1, the MIC values for all parent compounds ranged from 313 to 1250 μg/ml. It was found that there are no differences in the MICs values of the starting compounds assessed against the test microorganisms. Indeed, their MIC values were as follows: 1250 μg/ml against *S. aureus*; 625 μg/ml against *B. subtilis, E. coli, P. aeruginosa and C. albicans.* The only exception was found for the two aminoadamantanes (amantadine and rimantadine), with MIC values of 313 μg/ml against *P. aeruginosa*. Moreover, the anti-candidal action of rimantadine differed from the whole series with MIC of 313 μg/ml.

It should be mentioned that, despite the known significantly high antimicrobial potential of kojic acid, that tendency was not observed in our survey. According to our data, its activity varied from 625 to 1250 μg/ml against the examined microbial species.

Furthermore, in comparison, the kojyl hybrids **3-5** were found to be more effective (MICs: 31-625 μg/ml) than the corresponding parents against all strains, except for hybrid **5**. The latter was found to have exactly the same activity (MIC: 625 μg/ml) against *B. subtilis*, *E. coli*, *C. albicans* and two-fold higher effect against *S. aureus* and *P. aeruginosa* than oseltamivir.

This observation suggests that carbamate group could enhance the assessed activity. Indeed, amongst the tested hybrids, the kojyl carbamate of rimantadine (**4**) emerged with MIC values of 31-125 μg/mL. Excluding the results of tobramycin, it turned out that *S. aureus* and *B. subtilis* (Gram-positive) were most sensitive to compound **4**, with the lowest MIC value of 31 μg/ml. In addition, the hybrid **4** displayed a 4-fold more potent activity against the tested Gram-positive bacteria than against Gram-negative ones.

Table 1. *In vitro* antimicrobial activity of novel kojyl carbamates, parent molecules and the control drugs

Compound		**Y**	MIC (μg/ml)				
			S. aureus	*B. subt.*	*E. coli*	*P. aerug.*	*C. albicans*
	**3)**		250	125	250	125	250
	4)		31	31	125	125	125
	5)		625	625	625	313	625
Amantadine	Am		1250	625	625	313	625
Rimantadine	Rim		1250	625	625	313	313
Oseltamivir	Os		1250	625	625	625	625
Kojic acid	KA		1250	625	625	625	625
Tobramycin			15.6	1.0	19.5	*NT*	*NT*
Ketoconazole			*NT*	*NT*	*NT*	*NT*	7.8

NT-not tested

Furthermore, in a comparative *in vitro* study against *S. aureus*, tobramycin (MIC: 15.6 μg/ml) was two times more active than the highly active compound **4** (MIC: 31 μg/ml).

This finding is encouraging, since *S. aureus* has been recognized as one of the main resistant pathogens amongst Gram-positive bacteria that can cause diseases in humans. Additionally, staphylococcal food poisoning is a leading cause of gastroenteritis [46].

Interestingly, by comparison with the antimicrobial activity of the two hybrids containing aminoadamantane fragments (amantadine or rimantadine), compounds **3** and **4** respectively, the tested antibacterial activity was increased at the expense of compound **4** (except in the case against *P. aeruginosa*, where the MICs were the same). The presence of an aditional hydrophobic >CH-CH_3 group at hybrid **4** was advantageous, as this led to a 2 to 8-fold increase in its activity.

Moreover, the same substituent enhanced 2-fold the anti-Candidal activity of compound **4** (MIC: 125 μg/ml) over compound **3** (MIC: 250 μg/ml).

Thus, in view of these findings, we could consider the kojy carbamate **4** as the most promising antimicrobial agent.

CONCLUSIONS

In conclusion, the synthesis of three novel kojyl carbamates (compounds **3**-**5**) by preliminary activation of kojic acid was reported. The antimicrobial activities of the hybrid structures, as well as of their parent structures were evaluated *in vitro*.

Preliminary study revealed that the synthetically obtained hybrids (with exception of compound **5**) showed stronger antimicrobial activities *in vitro* than their parent compounds.

Kojyl carbamate of rimantadine (compound **4**) was found to be a highly potent compound. Importantly, it showed a MIC value of 31 μg/ml against both Gram-positive bacteria (*B. subtilis*, *S. aureus*), whereas Gram-negative bacteria and the tested fungus have the same MIC of 125 μg/ml, which were nearly four-fold lower than that of Gram-positive bacteria.

Thus, kojyl carbamate **4** could be considered as a promising antimicrobial agent.

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REFERENCES

1. World Health Organization. WHO estimates of the global burden of foodborne diseases: foodborne disease burden epidemiology reference group 2007-2015. No. 9789241565165. World Health Organization, 2015.
2. B. Özçelik, I. Gürbüz, T. Karaoglu, E. Yesilada, *Microbiol. Res.*, **164**, 545 (2009).
3. M. U. Gökçe, B. Özçelik, G. Bakır, T. Karaoglu, E. Bercin, N. Noyanalpan, *Arzneim.-Forsch./Drug Res*., **54**, 891 (2004).
4. D. Esquenazi, M. D. Wigg, M. F. S. Miranda, *Res. Microbiol*., **153**, 647 (2002).
5. P. Vijayan, C. Raghu, G. Ashok, S. A. Dhanaraj, B. Suresh, *Indian J. Med. Res.*, **120**, 24 (2004).
6. S. P. Vladimirova, D. L. Danalev, D. A. Marinkova, R. N. Raykova, D. S. Manova, S. R. Marinova, D. I. Marinova, S. A. Yaneva, *Bulg. Chem. Commun.*, **49**, Special issue E, 86 (2017).
7. S. C. Basappa, V. Sreenivasamurthy, H. A. B. Parpia, *J. Gen. Microbiol.*, **61**, 81 (1970).
8. A. B. Ariff, M. S. Salleh, B. Ghani, M. A. Hassan, G. Rusul, M. I. A. Karim, *Enzyme Microb. Technol.*, **19**, 545 (1996).
9. M. Y. Kwak, J. S. Rhee, *Appl. Microbiol. Biotechnol.*, **36**, 578 (1992).
10. K. Takamizawa, S. Nakashima, Y. Yahashi, B. K. Kubata, T. Suzuki, K. Kawai, H. Horitsu, *J. Ferment. Bioeng.*, **82**, 414 (1996).
11. B. S. Gould, *Biochem. J.*, **32**, 797 (1938).
12. R. Nandan, H. Polasa, *Indian J. Microbiol.*, **25**, 21 (1985).
13. K. Coupland Jr., W. G. Niehaus, *Exp. Mycol.*, **11**, 206 (1987).
14. S. A. El-Aasar, *Int. J. Agric. Biol.*, **8**, 468 (2006).
15. R. Bentley, *Nat. Prod. Rep.*, **23**, 1046 (2006).
16. J. Brtko, L. Rondahl, M. Fickova, D. Hudecova, V. Eybl, M. Uher, *Cent. Eur. J. Publ. Health*, **12**, 16 (2004).
17. G. A. Burdock, M. Soni, I. G. Carabin, *Regul. Toxic. Pharm.*, **33**, 80 (2001).
18. A. Beelik, *Adv. Carbohydr. Chem.*, **48**, 145 (1956).
19. G. J. Nohynek, D. Kirkland, D. Marzin, H. Toutain, C. Leclerc-Ribaud, H. Jinnai, *Food Chem. Toxicol.*, **42**, 93 (2004).
20. Y. Terabayashi, M. Sano, N. Yamane, J. Marui, K. Tamano, J. Sagara, M. Dohmoto, K. Oda, E. Ohshima, K. Tachibana, Y. Higa, S. Ohashi, H. Koike, M. Machida, *Fungal Genet. Biol.*, **47**, 953 (2010).
21. S. Emami, S. J. Hosseinimehr, S. M. Taghdisi, S. Akhlaghpoor, *Bioorg. Med. Chem. Lett*., **1**, 45 (2007).
22. K. Wang, P. F. Li, C. G. Han, L. Du, C. Liu, M.Hu , S.J. Lian, Y. X. Liu, *Radiat. Res.*, **182**, 666 (2014).

23. D. S. Yoo, J. Lee, S. S. Choi, H. S. Rho, D. H. Cho, W. C. Shin, J. Y. Cho, *Die Pharmazie - Int. J. Pharm. Sci.*, **65**, 261 (2010).
24. M. Uher, D. Hudecová, J. Brtko, J. Dobias, J. Kováč, E. Šturdík, V. Koneč-ný, Š. Varkonda, L. Ujhelzová, M. Pódová, J. Buchvlad, CS Patent No. 259592 (1989).
25. M. Uher, V. Konecny, O. Rajniakova, *Chem. Pap.-Chem. Zvesti*, **48**, 282 (1994).
26. D. Hudecová, M. Uher, J. Brtko, *Biologia*, **47**, 483 (1992).
27. R. M. Saleh, S. A. Kabli, S. M.Al-Garni, S. A. Mohamed, *Afr. J. Microbiol. Res*., **5**, 1619 (2011).
28. M. Saeedi, M. Eslamifar, K. Khezri, *Biomed. Pharmacother.*, **110**, 582 (2019).
29. M. Veverka, E. Kralovicova, *Coll. Czech. Chem. Commun.*, **55**, 833 (1990).
30. T. Tamura, K. Mitsumori, Y. Totsuka, K. Wakabayashi, R. Kido, H. Kasai, M. Nasu, M. Hirose, *Toxicol.*, **222**, 213 (2006).
31. Y. Wu, Y. G. Shi, L. Y. Zeng, Y. Pan, X. Y. Huang, L. Q. Bian, Y.-J. Zhu, R.-R. Zhang, J. Zhang, *Food Sci. Technol. Int.*, **25**, 3 (2019).
32. M. D. Aytemir, D. D. Erol, R. C. Hider, M. Ozalp, *Turk. J. Chem.*, **27**, 757 (2003).
33. A. Fassihi, D. Abedi, L. Saghaie, R. Sabet, H. Fazeli, G. Bostaki, O. Deilami, H. Sadinpour, *Eur. J. Med. Chem.*, **44**, 2145 (2008).
34. H. Kayahara, N. Shibata, K. Tadasa, H. Maeda, T. Kotani, I. Ichimoto, *Agr. Biol. Chem.*, **54**, 2441 (1990).
35. M. D. Aytemir, B. Özçelik, *Eur. J. Med. Chem.*, **45**, 4089 (2010).
36. J. Kim, P. K. Chang, K. Chan, N. Faria, N. Mahoney, Y. Kim, M. de L. Martins, B. Campbell, *Int. J. Mol. Sci.*, **13,** 13867 (2012).
37. J. Kim, B. Campbell, K. Chan, N. Mahoney, R. Haff, *Molecules*, **18**, 1564 (2013).
38. L. Wanka, K. Iqbal, P. R. Schreiner, *Chem. Rev.*, **113**, 3516 (2013).
39. D. L. Danalev, S. P. Vladimirova, B. P. Borisov, H. H. Nocheva, A. I. Bocheva, D. A. Marinkova, E. D. Naydenova, V. S. Lozanov, *Int. J. Pept. Res. Ther*., **22**, 243 (2016).
40. I. Stankova, K. Chuchkov, R. Chayrov, L. Mukova, A. Galabov, D. Marinkova, D. Danalev, *Int. J. Pept. Res. Ther*., 1 (2019), DOI: 10.1007/s10989-019-09983-4.
41. H. Kim, J. Choi, J. K. Cho, S. Y. Kim, Y. S. Lee, *Bioorg. Med. Chem. Lett.*, **14**, 2843 (2004).
42. J. C. Sheehan, G. P. Hess., *J. Am. Chem. Soc*., **77**, 1067 (1955).
43. J. M. Andrews, *J. Antimicrob.Chemother.*, **48**, 5 (2001).
44. J. Chaudhary, A. N. Pathak, S. Lakhawat, *Annu. Res. Rev. Biol.*, **4**, 3165 (2014).
45. A. K. Ghosh, M. Brindisi, *J. Med. Chem.*, **58**, 2895 (2015).
46. Y. Le Loir, F. Baron, M. Gautier, *Genet. Mol. Res.*, **2**, 63 (2003).