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Microwave-assisted synthesis of 1*H*-tetrazole-based flavonoid derivatives and their antimicrobial activity

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Abstract: A series of novel tetrazole scaffolds containing chalcones **4a**–**e** and aurones **5a**–**e** were synthesized under conventional and microwave irradiation conditions. All the newly synthesized compounds were characterized by IR, NMR and mass spectral data. Furthermore, the title compounds were screened *in vitro* for their antimicrobial activity against bacteria, such as *Staphylococus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae* and *Escherichia coli*, as well as fungi, such as *Aspergillus niger, A. flavus* and *Fusarium oxysporum*. Some of the compounds showed very good activity compared to standard drugs against all the tested pathogenic bacteria and fungi.

Keywords: 4-(1*H*-tetrazol-5-yl)benzaldehyde; chalcone; aurone; microwave irradiation; antimicrobial activity.

INTRODUCTION

Tetrazoles are a class of heterocyclic compounds containing four nitrogens and one carbon in a five-membered ring. Tetrazoles were found to possess various biological activities, such as antibacterial,[1,2] anticancer,[3] analgesic,[4] antitubercular,[5] antifungal[6] and anticonvulsant.[4] In addition, 1,5-disubstituted tetrazoles are used as anti-inflammatory and anti-hypertensive agents.[7,8] The tetrazole-containing diuretic agent 2-chloro-5-(1*H*-tetrazol-5-yl)-4-((thiophen-2--ylmethyl)amino)benzenesulfonamide **1** (azosemide)[9,10] is widely used in the complex therapy of hypertonic disease, whereas losartan **2** is an angiotensin II receptor antagonist drug used mainly to treat high blood pressure (hypertension),[11] while tetrazolo[1,5-*a*]quinolines **3** are novel anti-inflammatory and antibacterial agents[12] (Fig. 1).

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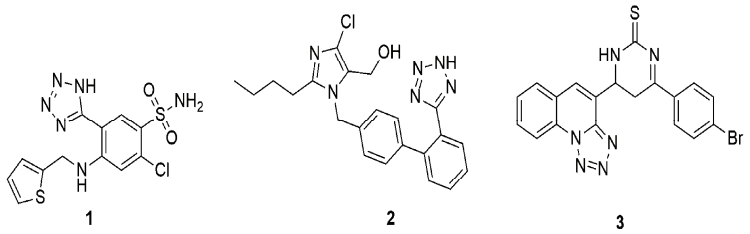


Fig. 1. Structures of tetrazole-containing drugs.

Chalcones are commonly used in the chemistry of natural products, as precursors in the synthesis of flavonoids[13,14] and various heterocyclic derivatives. Some chalcone derivatives are used as sweeteners, drugs and sunscreen agents.[15] Various substituted chalcones have been reported to possess antibacterial[16] antiulcer,[17] antifungal,[18] antioxidant,[19] vasodilatory,[20] antimitotic,[21] antimalarial[22] and antileishmanial,[23] and leukotriene B4,[24] inhibitory activities.

Aurones occur rarely in nature and are a less studied subclass of flavonoids. In aurones, the benzofuran component is associated with a benzylidene linked in the second position. Unlike flavonoids, which contain a six-membered ring, the aurone molecule contains a chalcone like group which is closed into a 5--membered ring. Aurones possess antifeedant,[25] anti-inflammatory,[26] anticancer,[27] antileishmanial,[28] antibacterial[29] and antioxidant activity,[19] and also show inhibitory activity against a variety of enzymes and proteins.[30,31]

Microwave irradiation has become an important technique in organic synthesis and has attracted the attention of researchers because of its various advantages, such as shorter reaction times, higher yields, consumption of small amount of energy,[32,33] experimental simplicity and selectivity over the conventional heating technique.

Inspired by the pharmacological summary of all these components some new tetrazole scaffolds containing chalcone derivatives **4a**–**e** and respective aurones **5a**–**e** were designed and synthesized using the microwave irradiation method, as well as the conventional method. Among the two methods, the microwave irradiation method proved to be environmentally benign and gave better yields with shorter reaction times compared to the conventional method.

EXPERIMENTAL

All the reagents and solvents were purchased from Sigma–Aldrich or S.D. Fine Chemicals Ltd. and used without further purification. Melting points were determined using a Cintex apparatus and are uncorrected. Elemental analysis was performed by means of Perkin Elmer 2400 CHN elemental analyzer. The purity of compounds was monitored by TLC on silica gel plates 60 F_{254} (Merck). Reactions under microwave irradiation were realized in a Milestone Multi-SYNTH microwave system. IR (KBr) spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Bruker

Avance II 400 MHz spectrometer (TMS internal standard). Mass spectra were recorded on a Shimadzu LCMS-2020 mass spectrometer using the electrospray ionization method (ESI).

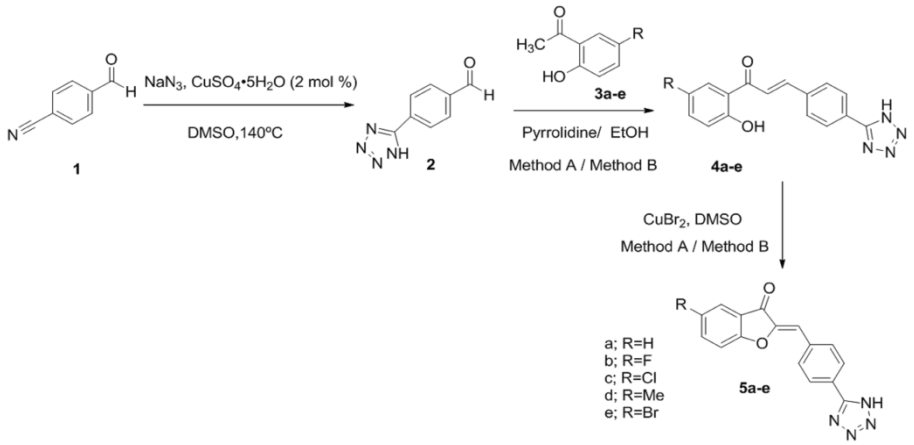
Spectral and analytical data are given as Supplementary material to this paper.

*4-(1*H*-Tetrazol-5-yl)benzaldehyde*[34] ***(2)***

Sodium azide (1 mmol) and cupric sulfate pentahydrate (2 mol %) were added to a stirred solution of 4-formylbenzonitrile **1** (1 mmol) in DMSO (2 mL) at room temperature. The reaction mixture was then heated at 140 °C for 1 h (Scheme 1). After completion of the reaction (monitored by TLC), the reaction mixture was cooled and treated with 1 M dilute HCl (10 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude compound. The crude product was washed with ethyl acetate:hexane (1:1) filtered and dried under vacuum to afford compound **2** as colorless crystals.

*General procedure for the synthesis of (*E*)-1-phenyl-3-(4-(1*H*-tetrazol-5-yl)phenyl)-prop-2-en--1-one analogues (**4a**–**e**)*

Conventional heating (method A). To a stirred mixture of 4-(1*H*-tetrazol-5-yl)benzaldehyde **2** (1 mmol) and a substituted acetophenone **3a**–**e** (1 mmol) in ethanol (4 mL) was added pyrrolidine (1 mmol) and the mixture was stirred at room temperature for 20–24 h. (Table I). After completion of the reaction (Scheme 1, monitored by TLC), the reaction mixture was diluted with ice water (50 mL), acidified with 1 M HCl, the precipitated solid filtered, washed with water and dried under vacuum to obtain the crude compound. The crude compound was recrystallized from ethanol to afford pure chalcone **4a**–**e**.



Scheme 1. Synthesis of chalcone **4a**–**e** and aurone **5a**–**e** derivatives using conventional (method A) and microwave irradiation (method B) methods.

Microwave irradiation (method B). A mixture of 4-(1*H*-tetrazol-5-yl)benzaldehyde 2 (1 mmol), substituted acetophenone **3a**–**e** (1 mmol) and pyrrolidine (1 mmol) in ethanol (4 mL) was subjected to microwave irradiation at 180 W for 8–11 min (Table I). The progress of the reaction (Scheme 1) was monitored by TLC. After completion of the reaction, the reaction mixture was diluted in cold water (50 mL), acidified with 1 M HCl, stirred for 10 min and the precipitated solid filtered off, washed with water and dried under vacuum. The resulting solid compound was recrystallized from ethanol to afford pure chalcone **4a**–**e**.

*General procedure for the synthesis of compounds (**5a**–**e**)*

Method A. To a stirred solution of cupric bromide (7.2 mmol) in DMSO (2 mL) was added chalcone derivative **4a**–**e** (10 mmol) at room temperature and refluxed for 6–8 h (Table I). After completion of the reaction, the mixture was poured into ice-cold water and extracted with dichloromethane (2×30 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum to obtain the crude compound. The crude compound was purified by column chromatography using ethyl acetate/ /hexane (7:3 volume ratio) as eluent to afford aurone **5a**–**e**.

Method B. A mixture of chalcone derivative **4a**–**e** (10 mmol), cupric bromide (7.2 mmol) in DMSO (2 mL) was taken in a quartz tube and inserted into a Teflon vial with a screw cap and subjected to microwave irradiation at 180 watts for 7–8 min (Table I). After completion of the reaction, the mixture was poured into ice-cold water and extracted with dichloromethane (2×30 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the crude compound. The crude compound was subjected to column chromatography using ethyl acetate/hexane (7:3 volume ratio) as eluent to obtain the pure aurone **5a**–**e**.

Biological assays

Antibacterial activity. All the synthesized compounds were screened *in vitro* for antibacterial activity against gram-positive organisms (*i.e.*, *Staphylococcus aureus* (ATCC 6538) and *Bacillus subtilis* (ATCC 6633)) and gram negative bacterial strains (*Klebsiella pneumoniae* (ATCC 13883) and *Escherichia coli* (ATCC 25922)) at 20 and 40 μg mL^{-1} concentrations (Table II).The bacterial cultures were grown in nutrient agar media and subcultured for the better growth in a liquid nutrient broth medium and further subcultured onto Petri plates for the experiments. The broth cultures were diluted with sterilized saline to bring the final size of inoculum to approximately to 10^5–10^6 CFU ml^{-1}. The compounds were dissolved in DMSO for the biological assays and pure solvent DMSO showed no inhibition zone. For disc diffusion method,[35] the test compound was introduced onto the disc and then allowed to dry. Once a disc was completely saturated with the test compound, it was introduced onto the upper layer of the medium containing the bacterial inoculums. The Petri dishes were incubated overnight at 37 °C for 24 h. The diameters of the zones of inhibition were measured to determine the antibacterial activity. Triplicates for all the compounds were run and the results are expressed as zone of inhibition in mm. The results for the newly synthesized compounds were compared with that for ciprofloxacin, as the standard antibiotic drug.

Antifungal activity.[36] All the compounds were screened *in vitro* for their antifungal activity against *Aspergillus niger* (ATCC 20057), *A. flavus* (ATCC 11497) and *Fusarium oxysporum* (ATCC-7601) using amphotericin-B as the standard drug. The test compounds were dissolved in DMSO before mixing with potato dextrose agar medium (PDA, 20 mL).[36] The final concentration of compounds in the medium was maintained to be 50μg mL^{-1}. Above--mentioned types of fungi were incubated in PDA at 25±1 °C for 3–4 days to obtained good mycelium growth for antifungal assay; then, amycelia disk of approximately 0.45 cm diameter cut from the culture medium was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. The inoculated plates were incubated at 25±1 °C for 5 days. DMSO in sterilized distilled water was used as control, while amphotericin-B was used as standards for all the treatment; three replicates were performed. The radial growth of the fungal colonies was measured on the fourth day, and the data were statistically analyzed. The *in vitro* inhibition effects of the test compounds on the fungi were calculated by the given formula $CV = A–B/A$, where A represents the diameter of fungi growth on untreated PDA (con-

trol of DMSO), *B* represents the diameter of fungi on treated PDA (diameter of synthetic compoundsv**4a**–**e** and **5a–e**)and *CV* represents the zone of inhibition.

RESULTS AND DISCUSSION

Chemistry

In the present work, a series of tetrazole chalcones and respective aurones as shown in a Scheme 1 were synthesized. 4-(1*H*-Tetrazol-5-yl)benzaldehyde (**2**) was obtained from 4-formylbenzonitrile (**1**) with sodium azide in the presence of $CuSO_4 \cdot 5H_2O$ in DMSO under stirring at room temperature. Then the reaction temperature was raised to 140 °C for 1 h. On treatment with different acetophenones (**3a**–**e**) in presence of pyrrolidine in ethanol, the required products were obtained but in low yields. The reaction that occurred under microwave irradiation gave better yields than the conventional methods. Furthermore, these 2′-hydroxy chalcones **4a**–**e** were oxidized with cupric bromide in the presence of DMSO, a five-membered transition state, which is favorable, formed, leading to the corresponding aurones **5a**–**e**. Thus, the microwave irradiation method proved to be environmentally benign and gave better yields in shorter reaction times (Table I).

TABLE I. Comparison of the yield of the synthesized compounds **4a**–**e** and **5a**–**e**

Product	Time of conventional synthesis, h	Time of MW synthesis, min	Yield, %		M. p., °C
			Conventional synthesis	MW synthesis	
4a	22	9	60	75	198–200
4b	20	11	65	77	206–208
4c	21	8	62	80	190–192
4d	23	9	63	79	182–184
4e	24	11	50	76	206–208
5a	6	8	65	72	156–158
5b	8	7	69	75	155–157
5c	7	8	60	73	150–152
5d	6	7	63	73	160–162
5e	7	8	65	76	154–156

All the newly synthesized scaffolds **4a**–**e** and 5**a**–**e** were characterized based on IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data, and elemental analysis.

As a representative example, the spectral data of one of the chalcone derivative **3b** is as follows. In the IR spectrum, the characteristic carbonyl absorption was observed at 1641 cm^{-1} (>C=O). The N–H absorption was observed at 3473 cm^{-1} while the OH absorption was observed at 3539 cm^{-1}. In the ^{1}H-NMR spectrum, the characteristic phenolic proton appeared as singlet at 12.26 ppm. The H_α proton of the conjugated α,β-unsaturated system appeared as doublet at 7.88 ppm with a coupling constant value of 15.41 Hz. All the signals for the rem-

aining protons are in the expected region and were in accord with the desired compound. In the ^{13}C-NMR spectrum, the characteristic carbonyl carbon signal appeared at 192.4 ppm. The carbon signal that appeared at 155.9 ppm corresponded to the tetrazole carbon.[34] The other signals were all in the expected region. In the mass spectrum, the base peak was observed at an *m*/*z* value of 311, which further confirmed the structure.

The spectral analysis of the aurone derivative **5c** was as follows. In the IR spectrum the carbonyl stretching resonated at 1670 cm^{-1} (>C=O). In the ^{1}H--NMR spectrum, the characteristic benzylidene proton appeared as a singlet at 6.85 ppm and all the remaining protons were in the expected region. In the ^{13}C--NMR spectrum, the signal that appeared at 175.6 ppm corresponds to the characteristic carbonyl carbon. The tetrazole carbon signal appeared at 155.8 ppm while the signal at 110.4 ppm corresponds to the characteristic benzylidene carbon. All the remaining carbon signals were in the expected region. The mass spectra of the compound showed the base peak at *m*/*z* 325, which further confirmed the structure.

Antibacterial activity

All the synthesized compounds **4a**–**e** and **5a**–**e** were screened *in vitro* for their antibacterial activity against gram-positive organisms, *i.e.*, *S. aureus* (ATCC 6538) and *B. subtilis* (ATCC 6633), and Gram-negative bacterial strains, *i.e.*, *K. pneumoniae* (ATCC 13883) and *E. coli* (ATCC 25922) at 20 and 40 μg mL^{-1} concentrations (Table II). The zone of inhibition was measured in mm, and ciprofloxacin was used as the standard antibacterial substance, under similar conditions for comparison.

TABLE II. Antibacterial activities (zone of inhibition, mm) of the newly synthesized compounds **4a–e** and **5a–e**

Compound	Gram-positive bacteria				Gram-negative bacteria			
	S. aureus		*B. subtilis*		*K. pneumoniae*		*E. coli*	
	Concentration of compounds in DMSO, μg mL^{-1}							
	20	40	20	40	20	40	20	40
4a	12	22	14	25	14	24	15	20
4b	13	23	13	24	6	25	15	20
4c	12	24	9	17	8	14	10	15
4d	10	20	9	15	6	14	7	18
4e	8	12	7	16	4	5	5	9
5a	13	23	12	26	20	22	14	24
5b	13	25	12	20	9	14	10	18
5c	11	22	10	14	9	14	8	15
5d	7	12	7	13	5	8	2	7
5e	11	20	8	14	8	12	8	11
Ciprofloxacin	15	28	16	30	23	35	18	35

Some of the synthesized compounds showed potent activity and some moderate activity compared to the standard drug ciprofloxacin at a concentration of 20 and 40 μg mL^{-1}. The compounds **4a**, **4b**, **5a** and **5b** showed potent activity for *S. aureus*, *B. subtilis*, *K. pneumoniae* and *E. coli*, compared to the standard drug at concentrations of 10 and 20 μg mL^{-1}. Compounds **4c**, **4d** and **5c** showed moderate activity and the other compounds **4e, 5d** and **5e** showed poor activity. It could also be concluded that changing the halogen substitution from F to Cl and Br did not lead to any significant changes in the antibacterial activity of compound **5** derivatives. On the contrary, for the compound **4** derivatives, there was a significant decrease in the antibacterial activity (Table II) on changing the halogen from F (**4b**) to Cl (**4c**) and from Cl (**4c**) to Br (**4e**).

Antifungal activity

The antifungal activity of synthesized compounds **4a**–**e** and **5a**–**e** was tested against three pathogenic fungi, *i.e.*, *A. niger, A. flavus* and *F. oxysporum* **(**Table III). The compounds **4b** and **5b** showed better activity than the standard drug against *A. niger*, *A. flavus* and *F. oxysporum*. The compounds **4a** and **5a** showed moderate activity compared to the standard drug against *A. flavus*, whereas the remaining compounds showed similar activity against pathogenic fungi compared to the standard amphotericin-B.

TABLE III. Antifungal activities (zone of inhibition, mm) of the newly synthesized compounds **4a**–**e** and **5a**–**e**

Compound	*Fungus*		
	A. niger	*A. flavus*	*F. oxysporum*
4a	4.6±0.7	13.6±0.5	5.5±0.9
4b	13.8±0.4	11.4±0.9	12.5±0.6
4c	4.5±0.1	6.5±1.2	8.4±1.1
4d	2.6±0.5	8.4±0.5	4.5±0.7
4e	8.6±0.4	8±0.3	7.2±0.9
5a	8.1±0.2	12.4±0.2	9±0.4
5b	12.8±0.6	10.5±0.6	13±0.9
5c	8.4±0.2	6.1±0.4	8.3±0.4
5d	4.6±0.7	8.1±0.1	4.5±0.1
5e	7.8±0.5	4.9±0.8	7.9±0.7
Amphotericin-B	14±0.3	12.5±0.2	15.2±0.9

In conclusion, compounds **4b** and **5b** with a fluoro substitution on the ring showed maximum activity against *A. flavus*, *A. niger* and *F. oxysporum*.

CONCLUSIONS

In conclusion, a novel series of tetrazoles containing chalcone **4a**–**e** and aurone **5a**–**e** derivatives were successfully synthesized by microwave irradiation in

excellent yields and shorter reaction times compared to the conventional method. Moreover, this synthesis approach provides a structural framework that could be explored further in the development of new aurones derivatives from chalcone moieties. All the new compounds were screened for their antimicrobial activity. Among the synthesized compounds, **4a**, **4b**, **5a** and **5b** were more active against the bacterial strains, whereas the compounds **4b** and **5b** were more potent against the tested pathogenic fungi compared to the standard drugs at the respective concentrations.

SUPPLEMENTARY MATERIAL

Analytical and spectral data are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА ДЕРИВАТА ФЛАВОНОИДА СА 1*H*-ТЕТРАЗОЛСКОМ СТРУКТУРОМ ОЗРАЧИВАЊЕМ МИКРО-ТАЛАСИМА И ЊИХОВА АНТИМИКРОБНА АКТИВНОСТ

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Синтетисана је серија нових халкона **4a**–**e** и аурона **5a**–**e** који садрже тетразолску структуру, под конвенционалним термалним и микроталасним реакционим условима. Сва нова једињења су окарактерисана ИЦ, NMR и масеним спектрима. Испитана је антимикробна активност синтетисаних једињења према бактеријама *Staphylococus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae* и *Escherichia coli*, као и антифунгална активност према *Aspergillus niger, A. flavus* и *Fusarium oxysporum*. Нека од синтетисаних јеињења показују веома добру активност у поређењу са лековима који су стандарди у испитивању антибактеријске и антифунгалне активности.

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REFERENCES

1. V. V. Mulwad, R. B. Pawar, A. C. Chaskar, *J. Korean Chem. Soc.* **52** (2008) 249
2. K. Kemajl, V. Idriz, H. Arben, G. Sevdije, I. Muharrem, M. Sefkija, *FASEB J.* **21** (2007) 790
3. V. H. Bhaskar, P. B. Mohite, *J. Optoelectron. Biomed. Mater*. **2** (2010) 249
4. A. Rajasekaran, N. Sankar, A. Murugeh, K. A. Rajagopal, *Arch. Pharm. Res*. **29** (2006) 535.
5. J. Adamec, K. Waisser, J. Kunes, J. Kaustova, *Arch. Pharm. (Weinheim, Ger.)* **338** (2005) 385
6. R. S. Upadhayaya, S. Jain, N. Sinha, N. Kishore, R. Chandra, S. K. Arora, *Eur. J. Med. Chem.* ***3*9** (2004) 579
7. R. J. Herr, *Bioorg. Med. Chem*. **10** (2002) 3379

8. P. B. Mohite, R. B. Pandhare, S. G. Khanage, V. H. Bhaskar, *J. Pharm. Res*. **3** (2010) 43
9. V. A. Ostrovskii, G. I. Koldobskii, R. E. Trifonov, *Compr. Heterocycl. Chem. III* **6** (2008) 257
10. K. Harada, H. Izawa, T. Nishizawa, A. Hirashiki, Y. Murase, M. Kobayashi, M. Yokota, *J. Cardiovasc. Pharmacol*. **53** (2009) 468
11. R. D. Larsen, A. O. King, C. Y. Chen, E. G. Corley, B. S. Foster, F. E. Roberts, T. R. Verhoeven, *J. Org. Chem.* **59** (1994) 6391
12. A. A. Bekhit, O. A. El-Sayed, E. Aboulmagd, J. Y. Park, *Eur. J. Med. Chem.* **39** (2004) 249
13. C. Dyrager, M. Wickstrom, M. Fridén-Saxin, A. Fridberg, K. Dahlén, E. Wallen, J. Gullbo, M. Grothli, K. Luthman, *Bioorg. Med. Chem*. **19** (2011) 2659
14. F. Chimenti, R. Fioravanti, A. Bolasco, P. Chimenti, D. Secci, A. Rossi, M. Yáñez, F. Orallo, F. Ortuso, S. Alcaro, *J. Med. Chem*. **52** (2009) 2818
15. J. T. Li, W. Z. Yang, S. X. Wang, S. H. Li, T. S. Li, *Ultrason. Sonochem*. **9** (2002) 237
16. X. L. Liu, Y. J. Xu, M. L. Go, *Eur. J. Med. Chem.* **43** (2008) 1681
17. J. J. Ares, P. E. Outt, J. L. Randall, J. N. Johnston, P. D. Murray, L. M. O'Brien, B. L. Ems, *Bioorg. Med. Chem. Lett.* **6** (1996) 995
18. K. L. Lahtchev, D. I. Batovska, S. P. Parushev, V. M. Ubiyvovk, A. A. Sibirny, *Eur. J. Med. Chem.* **43** (2008) 2220
19. A. Detsi, M. Majdalani, C. A. Kontogiorgis, D. Hadjipavlou-Litina, P. Kefalas, *Bioorg. Med. Chem*. **17** (2009) 8073
20. X. Dong, J. Chen, C. Jiang, T. Liu, Y. Hu, *Arch. Pharm. (Weinheim, Ger.)* **342** (2009) 428.
21. Y. K. Rao, S. H. Fang, Y. M. Tzeng, *Bioorg. Med. Chem. Lett.* **17** (2009) 7909
22. V. J. Ram, A. S. Saxena, S. Srivastava, S. Chandra, *Bioorg. Med. Chem. Lett.* **10** (2000) 2159
23. M. Liu, P. Wilairat, S. L. Croft, A. L. C. Tan, M. L. Go, *Bioorg. Med. Chem.* **11** (2003) 2729
24. H. K. Horng, T. T. Lo, L. Y. Kun, T. L. Cheng, P. W. Jih, N. L. Chun, *Bioorg. Med. Chem.* **11** (2003) 105
25. M. Morimoto, H. Fukumoto, T. Nozoe, A. Hagiwara, K. Komai, *J. Agric. Food Chem.* **55** (2007) 700
26. S. Y. Shin, M. C. Shin, J. S. Shin, Y. S. Lee, *Bioorg. Med. Chem. Lett*. **21** (2011) 4520
27. H. Cheng, L. Zhang, Y. Liu, S. Chen, H. Cheng, X. Lu, G. C. Zhou, *Eur. J. Med. Chem.* **45** (2010) 5950
28. O. Kayser, A. F. Kiderlen, *Tokai J. Exp. Clin. Med.* **23** (1998) 423
29. N. Hadj-Esfandiari, L. Navidpour, H. Shadnia, M. Amini, N. Samadi, M. A. Faramarzid, A. Shafiee, *Bioorg. Med. Chem. Lett.* **17** (2007) 6354
30. S. Okombi, D. Rival, S. Bonnet, A. M. Mariotte, E. Perrier, A. Boumendjel, *J. Med. Chem*. **49** (2006) 329
31. M. G. Thomas, C. Lawson, N. M. Allanson, B. W. Leslie, J. R. Bottomley, A. McBride, O. A. Olusanya, *Bioorg. Med. Chem. Lett.* **3** (2003) 423
32. L. Gilbert, C. Mercier, *Stud. Surf. Sci. Catal*. **78** (1993) 51
33. D. Ashok, M. Gandhi, G. Srinivas, A. V. Kumar, *Med. Chem. Res*. **23** (2014) 3005
34. B. Akhlaghinia, S. Rezazadeh, *J. Braz. Chem. Soc*. **23** (2012) 2197
35. M. R. Zaidan, A. Noor Rain, A. R. Badrul, A. Adlin, A. Norazah, I. Zakiah, *Trop Biomed*. **22** (2005) 165
36. D. Ashok, S. Ravi, A. Ganesh, B. Vijaya Lakshmi, S. Adam, S. D. S. Murthy, *Med. Chem. Res.* **25** (2016) 909.