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DEHYDROZINGERONE ANALOGUES: REACTION OF *O*-ALKYL DERIVATIVES OF VANILLIN AND METHYL CYCLOPROPYL KETONE

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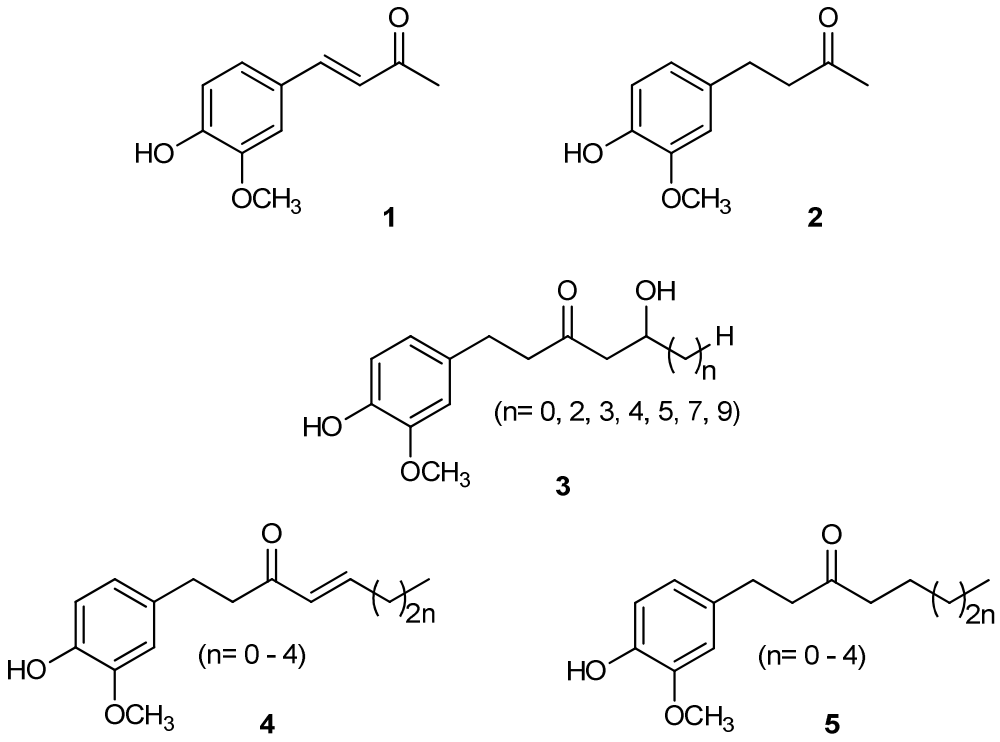
ABSTRACT. *O*-Alkyl vanillines and methyl cyclopropyl ketone reacts under Claisen-Schmidt conditions yielding corresponding enone derivatives, dehydrozingerone analogues with cyclopropane ring fragment, (*E*)-1-cyclopropyl-3-(4-alkoxy-3-methoxyphenyl)prop-2-en-1-ones. All new compounds were well characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and physical data.

Keywords: vanillin, enone system, dehydrozingerone, cyclopropyl.

INTRODUCTION

Chalcones and its derivatives exhibit various pharmacological and biological activities. They show good antimicrobial (OPLETALOVA, 2000; YAYLI *et al.*, 2006; TRIVEDI *et al.*, 2008), antifungal (MOSTAHAR *et al.*, 2007; LAHTCHEV *et al.*, 2008; BAG *et al.*, 2009), antioxidant (VOGEL *et al.*, 2008; SIVAKUMAR *et al.*, 2010; VASIL'EV *et al.*, 2010), antiprotozoal (LUNARDI *et al.*, 2003), antitrichomonal (OYEDAPO *et al.*, 2004), antimalarial (MOTTA *et al.*, 2006; LIM *et al.*, 2007; AWASTHI *et al.*, 2009), anti-inflammatory (HERENCIA *et al.*, 1998; ZHANG *et al.*, 2010) and anticancer activity (ROMAGNOLI *et al.*, 2008; ECHEVERRIA *et al.*, 2009; SZLISZKA *et al.*, 2009; ILANGO *et al.*, 2010). It is well known that free phenolic group in aromatic ring at position 4- was key factor important for strong antibacterial activity of numerous natural products (CHEN *et al.*, 1997; TSUKIYAMA *et al.*, 2002), beside of nature, position and number of substituent on aromatic rings.

Ginger root is excellent source for many kinds of active compounds. From ginger extracts have been isolated dehydrozingerone **1**, zingerone **2**, gingerols **3**, shogaols **4**, paradols **5** and their derivatives, with expressed bioactivity, such as anticancer, antioxidant, antimicrobial, anti-inflammatory, antidiabetic, anti-allergic (NAKAMURA and YAMAMOTO, 1983; DUGASANI *et al.*, 2010; SEMWAL *et al.*, 2015). Those compounds, similar to the chalcones, in their structure contains vanillin fragment.



Conjugate enone system which is presented in the dehydrozingerone is structurally different from chalcones; instead of the aryl group to the carbonyl is attached the methyl one. Their enone system could be easily transformed into some usable heterocyclic derivatives (ABDEL-RAHMAN *et al.*, 2007; KALIRAJAN *et al.*, 2009).

It is therefore, not surprising that many synthetic methods have been developed for the preparation of heterocycles starting from chalcone precursors that have been tested for their antimicrobial activities.

Knowing that cyclopropane ring is present in a huge number of natural isolated molecules (such as terpenes, fatty acids, alkaloids, steroids…) it is not a surprise that many of them show different biological activities, from enzyme inhibition of herpes proteases (PINTO *et al.*, 1996; WITVROUW *et al.*, 1999) to antibiotic, herbicidal, antitumor, and antiviral properties (BOGER *et al.*, 2001; FAUST, 2001; YOSHIDA *et al.*, 2004). Well known are chrysanthemic acid, pyrethrin and pyrethroid derivatives, compounds related to natural and synthetic insecticides, with good insecticidal activities (SAKAGUCHI *et al.*, 1998; CONCELLON *et al.*, 2007).

Starting from our previous results in dehydrozingerone derivatives transformation (RATKOVIĆ *et al.*, 2016), we want to prepare some dehydrozingerone analogues with alicyclic cyclopropane ring fragment. The first step was alkylation of free phenolic group in vanillin **6** and second one was Claisen-Schmidt condensation of obtained *O*-alkyl derivatives **7a-f** with methyl cyclopropyl ketone, Scheme 1. Compounds **8a-f**, (*E*)-1-cyclopropyl-3-(4-alkoxy-3-methoxyphenyl)prop-2-en-1-ones were synthesized.

All new products were characterized by their spectral data (IR, ^{1}H NMR and ^{13}C NMR).

MATERIALS AND METHODS

General remarks

All starting chemicals were commercially available and used as received, except that the solvents were purified by distillation. Chromatographic separations were carried out using silica gel 60 (Merck, 230-400 mesh ASTM) whereas silica gel on Al plates, layer thickness 0.2 mm (Merck), was used for TLC. IR spectra were recorded on a Perkin-Elmer One FT-IR spectrometer with a KBr disc, ν in cm cm^{-1}; NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C), using $CDCl_3$ as solvent and TMS as the internal standard. ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million (ppm) and were referenced to the solvent peak; $CDCl_3$ (7.26 ppm for ^{1}H and 76.90 ppm for ^{13}C). Multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (*J*) are in Hertz (Hz).

Experimental procedure

1. Chemistry

Starting from vanillin **6**, set of its *O*-alkyl derivatives, compounds **7a-f**, was prepared by alkylation of free phenolic group with corresponding alkyl halides, following the previously described literature procedures, (OYEDAPO *et al.*, 2004; KATRITZKY *et al.*, 2006; TATSUZAKI *et al.*, 2006). *O*-Alkyl vanillines and methyl cyclopropyl ketone reacts under basic conditions (Claisen-Schmidt condensation) yielding corresponding enone compounds, (*E*)-1-cyclopropyl-3-(4-alkoxy-3-methoxyphenyl)prop-2-en-1-ones, **8a-f** in good yield, Scheme 1. Compounds **8a-f** was prepared following previously described procedure (FRINGUELLI *et al.*, 1994, 1995) and to slightly modified procedure (HAMADA and SHARSHIRA, 2011).

Compounds **8a** and **8f** are known compounds and their chemical synthesis was published earlier (COGNACQ, 1978; KUMAR and DHAR, 1995), while compounds **8b-e** are new compound and their structure and spectral data are given.

2. Chemical synthesis

*2.1. General procedure for synthesis of (*E*)-1-cyclopropyl-3-(4-alkoxy-3-methoxyphenyl)prop-2-en-1-one, **8a-f***

NaOH (3 g) was dissolved in 20 mL of water and cooled to 15 °C and 15 mL of ethanol was added. Into a cold solution, with intensive stirring, methyl cyclopropyl ketone (10 mmol in 5 mL of ethanol) was added dropwise during 30 min. Reaction mixture was kept at temperature under 20 °C. Corresponding *O*-alkyl vanillin (10 mmol) was dissolved in a 10 mL of ethanol and added dropwise into a reaction mixture and stirred for next 6 h. Then mixture is left overnight in refrigerator. Product crystallize from 60% ethanolic solution as white powder.

The separated solid was filtered, washed with water, dried and recrystallized from ethanol.

In some cases, products do not separate as solid. Following procedure was applied to isolate them: ethanol from reaction mixture was evaporated under reduced pressure while product remains as oily residue. Products were extracted with CH_2Cl_2 (3×50 mL); organic

layer was washed with water and dried over anhydrous Na_2SO_4. Solvent was distilled off and products crystallize in some cases on standing or from ether.

*2.1.1. Synthesis of (*E*)-1-cyclopropyl-3-(3,4-dimethoxyphenyl)prop-2-en-1-one,* ***8a***

Yield: 78.2% (1.81 g); m.p. 89-90 °C

^{1}H NMR ($CDCl_3$): 0.91-0.99 (m, 2H), 1.12-1.19 (m, 2H), 2.19-2.31 (m, 1H), 3.92 (s, 3H), 3.93 (s, 3H), 6.77 (d, *J* = 16 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 7.09-7.18 (m, 2H), 7.58 (d, *J* = 16.2 Hz, 1H); **^{13}C NMR ($CDCl_3$)**: 11, 19.4, 55.9, 56.0, 109.8, 111.1, 122.9, 124.6, 127.7, 142, 149.3, 151.2, 199.8; **IR (KBr)**: 3435, 2969, 2938, 2838, 1639, 1621, 1597, 1513, 1467, 1439, 1425, 1394, 1269, 1203, 1164, 1141, 1020, 985, 910, 875, 812, 802 cm^{-1}

*2.1.2. Synthesis of (*E*)-1-cyclopropyl-3-(4-ethoxy-3-methoxyphenyl)prop-2-en-1-one,* ***8b***

Yield: 76.8% (1.89 g); m.p. 77-78 °C

^{1}H NMR ($CDCl_3$): 0.91-0.99 (m, 2H), 1.11-1.19 (m, 2H), 1.49 (t, *J* = 7 Hz, 3H), 2.19-2.31 (m, 1H), 3.91 (s, 3H), 4.14 (q, *J* = 7 Hz, 2H), 6.76 (d, *J* = 16 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 7.10-7.15 (m, 2H), 7.57 (d, *J* = 16.2 Hz, 1H); **^{13}C NMR ($CDCl_3$)**: 10.9, 14.6, 19.3, 55.9, 64.3, 110.1, 112.2, 122.8, 124.4, 127.4, 142, 149.4, 150.6, 199.7; **IR (KBr)**: 3435, 3011, 2981, 2923, 2874, 1645, 1620, 1596, 1512, 1471, 1425, 1392, 1314, 1265, 1231, 1204, 1177, 1165, 1149, 1034, 983, 904, 869, 800 cm^{-1}

*2.1.3. Synthesis of (*E*)-1-cyclopropyl-3-(3-methoxy-4-isopropoxyphenyl)prop-2-en-1-one,* ***8c***

Yield: 74.6% (1.94 g); m.p. 56-57 °C

^{1}H NMR ($CDCl_3$): 0.91-1.00 (m, 1H), 1.12-1.19 (m, 1H), 1.40 (d, *J* = 6Hz, 6H), 2.17-2.31 (m, 1H), 3.89 (s, 3H), 4.53-4.67 (m, 1H), 6.76 (d, *J* = 16 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 7.10-7.15 (m, 2H), 7.57 (d, *J* = 16 Hz, 1H); **^{13}C NMR ($CDCl_3$)**: 11, 19.4, 22, 56, 71.3, 110.7, 114.6, 122.7, 124.5, 127.6, 142.1, 149.8, 150.4, 199.8; **IR (KBr)**: 3435, 3004, 2983, 2938, 1645, 1595, 1509, 1461, 1424, 1395, 1385, 1315, 1265, 1232, 1207, 1165, 1152, 1112, 1087, 1034, 985, 946, 906, 874, 820 cm^{-1}

*2.1.4. Synthesis of (*E*)-1-cyclopropyl-3-(3-methoxy-4-propoxyphenyl)prop-2-en-1-one,* ***8d***

Yield: 58.5% (1.52 g); m.p. 61 °C

^{1}H NMR ($CDCl_3$): 0.91-1.00 (m, 1H), 1.05 (t, *J* = 7.4Hz, 3H), 1.12-1.19 (m, 2H), 1.79-1.89 (m, 2H), 2.19-2.31 (m, 1H), 3.91 (s, 3H), 4.02 (t, *J* = 6.8 Hz, 2H), 6.76 (d, *J* = 16 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 7.10-7.16 (m, 2H), 7.57 (d, *J* = 16.2 Hz, 1H); **^{13}C NMR ($CDCl_3$)**: 10.3, 11, 11.1, 19.3, 56, 110.3, 112.4, 122.9, 124.4, 127.4, 142.1, 149.6, 150.9, 199.8; **IR (KBr)**: 3436, 2961, 2946, 2932, 2871, 1671, 1606, 1595, 1510, 1466, 1424, 1390, 1261, 1233, 1196, 1165, 1143, 1100, 1090, 1006, 806 cm^{-1}

*2.1.5. Synthesis of (*E*)-1-cyclopropyl-3-(3-methoxy-4-buthoxyphenyl)prop-2-en-1-one,* ***8e***

Yield: 58.5% (1.52 g); m.p. 56-57 °C

^{1}H NMR ($CDCl_3$): 0.91-1.07 (m, 2H), 0.98 (t, 3H, *J* = 7.2 Hz), 1.13-1.28 (m, 2H), 1.41-1.59 (m, 2H), 1.77-1.92 (m, 2H), 2.19-2.31 (m, 1H), 3.90 (s, 3H), 4.06 (t, *J* = 6.8 Hz, 2H), 6.76 (d, *J* = 16 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 7.10-7.15 (m, 2H), 7.57 (d, *J* = 16.2 Hz, 1H); **^{13}C NMR ($CDCl_3$)**: 10.9, 13.8, 19.1, 19.3, 31.0, 55.9, 68.7, 110.3, 112.4, 122.9, 124.4,

127.4, 142.1, 149.5, 150.9, 199.8; **IR (KBr)**: 2961, 2937, 2872, 1647, 1620, 1596, 1512, 1464, 1425, 1393, 1261, 1230, 1178, 1165, 1143, 1032, 984, 903, 799 cm^{-1}

*2.1.6. Synthesis of (*E*)-1-cyclopropyl-3-(4-benzyloxy-3-methoxyphenyl)prop-2-en-1-one, **8f***

Yield: 80.2% (2.47 g); m.p. 110-111 °C

^{1}H NMR ($CDCl_3$): 0.89-0.99 (m, 2H), 1.11-1.18 (m, 2H), 2.17-2.29 (m, 1H), 3.92 (s, 3H), 5.18 (s, 2H), 6.75 (d, *J* = 16. Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 7.04-7.11 (m, 2H), 7.29-7.46 (m, 5H), 7.55 (d, *J* = 16 Hz, 1H); **^{13}C NMR ($CDCl_3$):** 11, 19.4, 56, 70.8, 110.4, 113.5, 122.7, 124.7, 127.2, 128, 128.6, 136.5, 141.9, 149.8, 150.3, 199.8; **IR (KBr):** 3436, 3064, 3038, 3000, 2906, 2864, 1636, 1596, 1511, 1468, 1450, 1398, 1349, 1315, 1269, 1230, 1204, 1167, 1141, 1085, 1022, 971, 908, 807, 744, 732, 697, 565 cm^{-1}.

RESULTS AND DISCUSSION

Dehydrozingerone analogues, possessing cyclopropyl group attached to carbonyl, were synthesized under Claisen–Schmidt conditions, starting from *O*-alkylated vanillines and methyl cyclopropyl ketone, yielding corresponding enone compounds (*E*)-1-cyclopropyl-3-(4-alkoxy-3-methoxyphenyl)prop-2-en-1-one, **8a-f** in good yield, suitable for further transformation.

References:

[1] ABDEL-RAHMAN, A.A.H., ABDEL-MEGIED, A.E.S., HAWATA, M.A.M., KASEM, E.R., SHABAAN, M.T. (2007): Synthesis and antimicrobial evaluation of some chalcones and their derived pyrazoles, pyrazolines, isoxazolines and 5,6-dihydropyrimidine-2-(1*H*)-thiones. *Monatshefte* **138**: 889-897.

[2] AWASTHI, S.K., MISHRA, N., KUMAR, B., SHARMA, M., BHATTACHARYA, A., MISHRA, L.C., BHASIN, V.K. (2009): Potent antimalarial activity of newly synthesized substituted chalcone analogs *in vitro*. *Med. Chem. Res*. **18**: 407-420.

[3] BAG, S., RAMAR S., DEGANI, M.S. (2009): Synthesis and biological evaluation of *α,β*-unsaturated ketone as potential antifungal agents. *Med. Chem. Res*. **18**: 309-316.

[4] BOGER, D.L., HUGHES, T.V., HEDRICK, M.P., (2001): Synthesis, chemical properties, and biological evaluation of CC-1065 and Duocarmycin analogues incorporating the 5-methoxycarbonyl-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one alkylation sub-unit. *J. Org. Chem*. **66**: 2207-2216.

[5] CHEN, M., CHRISTENSEN, S.B., ZHAI, L., RASMUSSEN, M.H., THEANDER, T., FROKJAER, S., STEFFANSEN, B., DAVIDSEN, J., KHARAZMI, A. (1997): The novel oxygenated chalcone, 2,4-dimethoxy-4'-butoxychalcone, exhibits potent activity against human malaria parasite *Plasmodium falciparum* in vitro and rodent parasites *Plasmodium berghei* and *Plasmodium yoelii* in vivo. *J. Infect. Dis*. **176**: 1327-1333.

[6] COGNACQ, J-C. (1978): 1-(Aryloxy)-3-amino-2-propanols. *Ger. Offen*. DE 2736106 A1 19780223.

[7] CONCELLON, J.M., RODRIGUEZ-SOLLA, H., SIMAL, C. (2007): The first cyclopropanation reaction of unmasked *α,β*-unsaturated carboxylic acids: Direct and complete stereospecific synthesis of cyclopropanecarboxylic acids promoted by Sm/CHI_3. *Org. lett*. **9**: 2685-2688.

[8] DUGASANI, S., PICHIKA, M. R., NADARAJAH, V.D., BALIJEPALLI, M.K., TANDRA, S., KORLAKUNTA, J.N. (2010): Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *J. Ethnopharmacol*. **127**: 515-520.

[9] ECHEVERRIA, C., SANTIBANEZ, J.F., DONOSO-TAUDA, O., ESCOBAR, C.A., TAGLE, R.R. (2009): Structural antitumoral activity relationships of synthetic chalcones. *Int. J. Mol. Sci*. **10**: 221-231.

[10] FAUST, R. (2001): Fascinating fatural and artificial cyclopropane architectures. *Angew. Chem. Int. Ed*. **40**: 2251-2253.

[11] FRINGUELLI, F., PANI, G., PIERMATTI, O., PIZZO, F. (1994): Condensation reactions in water of active methylene compounds with arylaldehydes. One-pot synthesis of flavonols. *Tatrahedron* **50**: 11499-11508.

[12] FRINGUELLI, F., PANI, G., PIERMATTI, O., PIZZO, F. (1995): Epoxidation of *α,β*-unsaturated ketones in water. An environmentally benign protocol. *Life Chem. Rep*. **13**: 133-140.

[13] HAMADA, N.M.M., SHARSHIRA, E.M. (2011): Synthesis and antimicrobial evaluation of some heterocyclic chalcone derivatives. *Molecules* **16**: 2304-2312.

[14] HERENCIA, F., FERRANDIZ, M.L., UBEDA, A., DOMINGUEZ, J.N., CHARRIS, E.J., LOBO, G.M., ALCARAZ, M.J. (1998): Synthesis and anti-inflammatory activity of chalcone derivatives. *Bioorg. Med. Chem. Lett*. **8**: 1169-1174.

[15] ILANGO, K., VALENTINA, P., SALUJA, G. (2010): Synthesis and *in vitro* anticancer activity of some substituted chalcones derivatives. *Res. J. Pharm. Biol. Chem. Sci*. **1**: 354-359.

[16] KALIRAJAN, R., SIVAKUMAR, S.U., JUBIE, S.; GOWRAMMA, B., SURESH, B. (2009): Synthesis and biological evaluation of some heterocyclic derivatives of chalcones. *Int. J. ChemTech. Res*. **1**: 27-34.

[17] KATRITZKY, A.R., LONG, Q., HE, H., QIUA, G., WILCOX, A.L. (2006): Preparation of 2-alkoxy-5-methoxybenzaldehydes and 2-ethoxy-5-alkoxybenzaldehydes. *Arkivoc* (**vi**): 868-875.

[18] KUMAR, E.S., DHAR, D.N. (1995): Reaction of styryl cyclopropyl ketones with chlorosulfonyl isocyanate: Formation of iminosulfonyl chloride. *Ind. J. Chem. 34B* **1**: 63-64.

[19] LAHTCHEV, K.L., BATOVSKA, D.I., PARUSHEV, S.P., UBIYVOVK, V.M., SIBIRNY, A.A. (2008): Antifungal activity of chalcones: a mechanistic study using various yeast strains. *Eur. J. Med. Chem*. **43**: 2220-2228.

[20] LIM, S. S., KIM, H. S., LEE, D. U. (2007): *In vitro* antimalarial activity of flavonoids and chalcones, *Bull. Korean Chem. Soc*. **28**: 2495-2497.

[21] LUNARDI, F., GUZELA, M., RODRIGUES, A. T., CORRE, R., EGER-MANGRICH, I., STEINDEL, M., GRISARD, E.C., ASSREUY, J., CALIXTO, J.B., SANTOS, A.R.S. (2003):

Trypanocidal and leishmanicidal properties of substitution-containing chalcones, *Antimicrob. Agents Chemother*. **47**: 1449-1451.

[22] MOSTAHAR, S., KATUN, P., ISLAM, A. (2007): Synthesis of two vanillin ring containing flavones by different methods and studies of their antibacterial and antifungal activities. *J. Biol. Sci*. **7**: 514-519.

[23] MOTTA, L.F., GAUDIO, A.C., TAKAHATA, Y. (2006): Quantitative structure-activity relationships of a series of chalcone derivatives (1,3-diphenyl-2-propen-1-one) as anti-*Plasmodium falciparum* agents (anti malaria agents). *Internet Electron. J. Mol. Des*. **5**: 555-569.

[24] NAKAMURA, H., YAMAMOTO, T. (1983): The active part of the [6]-gingerol molecule in mutagenesis. *Mutat. Res. Lett*. **122**: 87-94.

[25] OPLETALOVA, V. (2000): Chalcones and their heterocyclic analogs as potential therapeutic agents in bacterial diseases. *Cesk. Slov. Farm*. **49**: 278-284.

[26] OYEDAPO, A.O., MANKANJU, V.O., ADEWUNMI, C.O., IWALEWA, E.O., ADENOWO, T.K. (2004): Antitrichomonal activity of 1,3-diaryl-2-propen-1-ones on *Trichomonas gallinae*. *Afr. J. Trad. CAM* **1**: 55-62.

[27] PINTO, I.L., WEST, A., DEBOUCKM, C.M., DILELLA, A.G., GORNIAK, J.G., O'DONNELL, K.C., O'SHANNESSY, D.J., PATEL, A., JARVEST, R.L. (1996): Novel, selective mechanism-based inhibitors of the herpes proteases. *Bioorg. Med. Chem. Lett*. **6**: 2467-2472.

[28] RATKOVIĆ, Z., MUŠKINJA, J., BURMUDŽIJA, A., RANKOVIĆ, B., KOSANIĆ, M., BOGDANOVIĆ, G. A., SIMOVIĆ-MARKOVIĆ, B., NIKOLIĆ, A., ARSENIJEVIĆ, N., ĐORĐEVIC, S., VUKIĆEVIĆ, R.D. (2016): Dehydrozingerone based 1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazoles: Synthesis, characterization and anticancer activity. *J. Mol. Struct*. **1109**: 82-88.

[29] ROMAGNOLI, R., BARALDI, P.G., CARRION, M.D., CARA, C.L., CRUZ-LOPEZ, O., PRETI, D. (2008): Design, synthesis, and biological evaluation of thiophene analogues of chalcones. *Bioorg. Med. Chem*. **16**: 5367-5376.

[30] SAKAGUCHI, K., MANO, H., OHFUNE, Y. (1998): Syntheses of optically active 2-substituted cyclopropanecarboxylic acids from chiral α-hydroxysilane derivatives. *Tetrahedron Lett*. **39**: 4311-4312.

[31] SEMWAL, R.B., SEMWAL, D.K., COMBRINCK, S., VILJOEN, A.M. (2015): Gingerols and shogaols: Important nutraceutical principles from ginger. *Phytochemistry* **117**: 554-568.

[32] SIVAKUMAR, P.M., PRABHAKAR, P.K., DOBLE, M. (2010): Synthesis, antioxidant evaluation and quantitative structure activity relationship studies of chalcones. *Med. Chem. Res*. **19**: 1-17.

[33] SZLISZKA, E., CZUBA, Z.P., MAZUR, B., SEDEK, L., PARADYSZ, A., KROL, W. (2009): Chalcones enhance TRAIL-induced apoptosis in prostate cancer cells. *Int. J. Mol. Sci*. **11**: 1-13.

[34] TATSUZAKI, J., BASTOW, K.F., NAKAGAWA-GOTO, K., NAKAMURA, S., ITOKAWA, H., LEE, K. (2006): Dehydrozingerone, chalcone, and isoeugenol analogues as *in vitro* anticancer agents. *J. Nat. Prod*. **69**: 1445-1449.

[35] TRIVEDI, A.R., DODIYA, D.K., RAVAT, N.R., SHAH, V.H. (2008) Synthesis and biological evaluation of some new pyrimidines *via* a novel chalcone series. *Arkivoc* (**xi**): 131-141.

[36] TSUKIYAMA, R.I., KATSURA, H., TOKURIKI, N., KOBAYASHI, M. (2002): Antibacterial activity of licochalcone A against spore-forming bacteria. *Antimicrob. Agents Chemother*. **46**: 1226-1230.

[37] VASIL'EV, R.F., KANCHEVA, V.D., FEDOROVA, G.F., BATOVSKA, D.I., TROFIMOV, A.V. (2010): Antioxidant activity of chalcones: The chemiluminescence determination of the reactivity and the quantum chemical calculation of the energies and structures of reagents and intermediates. *Kinet. Katal*. **51**: 507-515.

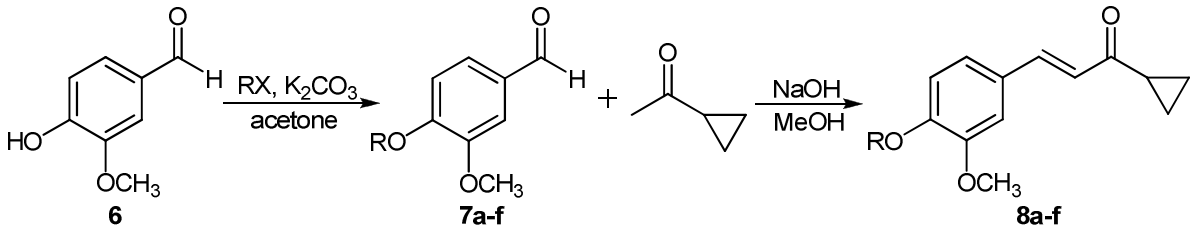
[38] VOGEL, S., OHMAYER, S., BRUNNER, G., HEILMANN, J. (2008): Natural and non-natural prenylated chalcones: Synthesis, cytotoxicity and antioxidative activity. *Bioorg. Med. Chem*. **16**: 4286-4293.

[39] WITVROUW, M., PANNECOUQUE, C., CLERCQ, E.D., FERNANDEZ-ALVAREZ, E., MARCO, J.L. (1999): Inhibition of human immunodeficiency virus type (HIV-1) replication by some diversely functionalized spirocyclopropyl derivatives. *Arch. Pharm*. **332**: 163-166.

[40] YAYLI, N., UCUNCU, O., YASAR, A., KUCUK, M., AKYUZ, E, KARAOGLU, S.A. (2006): Synthesis and biological activities of *N*-alkyl derivatives of *o*-, *m*-, and *p*-nitro (*E*)-4-azachalcones and stereoselective photochemistry in solution with theoretical calculations. *Turk. J. Chem*. **30**: 505-514.

[41] YOSHIDA, S., ROSEN, T.C., MEYER, O.G.J., SLOAN, M.J., YE, S., HAUFE, G., KIRK, K.L. (2004): Fluorinated phenylcyclopropylamines. Part 3: Inhibition of monoamine oxidase A and B. *Bioorg. Med. Chem*. **12**: 2645-2652.

[42] ZHANG, X.W., ZHAO, D.H., QUAN, Y.C., SUN, L.P., YIN, X.M., GUAN, L.P. (2010): Synthesis and evaluation of anti-inflammatory activity of substituted chalcone derivatives. *Med. Chem. Res*. **19**: 403-412.



6 **7a-f** **8a-f**

a) R=CH_3, b) R=C_2H_5, c) R=*i*-C_3H_7, d) R=C_3H_7, e) R=C_4H_9, f) R=$C_6H_5CH_2$

Scheme 1. Synthesis of (*E*)-1-cyclopropyl-3-(3-alkoxy-4-methoxyphenyl)prop-2-en-1-one, **8a-f**