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2,3,5-Trichlorocyclopent-2-enone derivatives in the Friedel–Crafts reaction with methoxybenzenes and the anticancer activity of the products

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Experimental section

The IR spectra were recorded in CH_2Cl_2 on a Shimadzu IR Prestige-21 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on Bruker AM-300 (300.13 and 75.47 MHz, respectively) and Bruker Avance-500 instruments (500.13 and 125.77 MHz) using tetramethylsilane as internal standard. The mass spectra (electron impact, 70 eV) were obtained an LCMS-2010EV mass spectrometer (Shimadzu) (sample solution in chloroform/acetonitrile were injected by a syringe at a flow rate of 0.1 ml min^{-1}, eluent was acetonitrile/water, 95:5) in the register mode of positive ions when the ionizing potential of the needle electrode 4.5 kV (the temperature of capillary interface is 250°C, the voltage of capillary interface is 5 V. Flow rate of atomizing gas (nitrogen) 1.5 dm^3 min^{-1} for chemical ionization at atmospheric pressure). Elemental analysis of synthesized compounds was obtained on the EURO EA-2000 CHNS analyzer. The reaction course was monitored by TLC on "Sorbphil" plates (Russia) with visualization of compounds by treatment with an alkaline solution of potassium permanganate. The products were isolated by column chromatography using Macherey-Nagel silica gel (Germany), 30–60 g per gram of substrate; freshly distilled solvents were used as eluents.

2-Allyl-2,4-dichloro-5-(2,4,6-trimethoxyphenyl)cyclopent-4-ene-1,3-dione **2a.** 1,3,5-Trimethoxybenzene (75.6 mg, 0.35 mmol) and $SnCl_4$ (0.08 ml) were added to a stirred solution of trichlorocyclopentenone **1a** (0.1 g, 0.35 mmol) in dichloroethane (20 ml), the reaction mixture was refluxed 5 h (TLC comtrol). The reaction mass then was cooled to room temperature, of distilled water (15 ml) was added, then diluted with $CHCl_3$ (15 ml). The organic layer was separated, washed with a saturated $NaHCO_3$ solution (2×15 ml), dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (EtOAc–petroleum ether, 1:10). Yield 0.11 g (85%). Bright yellow crystals, m.p. 115-116°C. IR (ν/cm^{-1}): 1723, 1610, 1584, 1472, 1457, 1419, 1287, 1229, 1207, 1165, 1152, 1131. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.90 (dd, 2H, CH_2, *J* 3.7 and 7.3 Hz,), 3.74 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.17 (dd, 2H, $=CH_2$, *J* 17.1 and 9.9 Hz,), 5.62 (ddd, 1H, =CH, *J* 7.3, 10.0 and

17.3 Hz,), 6.16 (s, 1H, H-Ar), 6.17 (s, 1H, H-Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.8 (CH_2), 55.5 (OCH_3), 55.8 (OCH_3), 61.7 (C^2), 90.8 and 90.9 (C^3_{Ar}, C^5_{Ar}), 97.6 (C^1_{Ar}), 121.7 (=CH_2), 128.9 (=CH), 151.1 (C^5), 151.9 (C^4), 158.9, 159.2, 164.5 (C^2_{Ar}, C^4_{Ar}, C^6_{Ar}), 189.9 (C=O), 191.6 (C=O). MS (EI), *m/z* (%): 371 (372, 373) $[MH]^+$ (100), 355 (356, 357) $[M - CH_3]^+$ (45). Found (%) C, 55.35; H, 4.21; Cl, 19.48. Calc. for $C_{17}H_{16}Cl_2O_5$ (%): C, 55.0; H, 4.34; Cl, 19.10.

2,4-Dichloro-5-(2,4,6-trimethoxyphenyl)-2-(2-methylbut-3-en-2-yl)cyclopent-4-ene-1,3-dione **3a** prepared similarly to **2a** from **1b** (0.1 g, 0.32 mmol) and 1,3,5-trimethoxybenzene (53 mg, 0.32 mmol). Yield 74 mg (58%). Yellow crystals, m.p. 109-111°C. IR (ν/cm^{-1}): 2973, 2943, 1758, 1716, 1613, 1584, 1493, 1471, 1464, 1417, 1343, 1285, 1229, 1207, 1163, 1132, 1057, 1035, 923, 816, 757. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.30 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.17 (dd, 2H, =CH_2, *J* 17.4 and 10.9 Hz), 5.62 (dd, 1H, =CH, *J* 17.2 and 10.8 Hz), 6.18 (s, 2H, H-Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.9 (CH_3), 23.0 (CH_3), 43.5 ($\underline{C}Me_2$), 55.5 (OCH_3), 55.7 (OCH_3), 55.8 (OCH_3), 69.5 (C^2), 90.9 and 90.5 (C^3_{Ar}, C^5_{Ar}), 97.2 (C^1_{Ar}), 115.2 (=CH_2), 140.7 (=CH), 151.1 (C^5), 151.4 (C^4), 159.1, 159.2, 164.3 (C^2_{Ar}, C^4_{Ar}, C^6_{Ar}), 190.2 (C=O), 191.7 (C=O). MS (EI), *m/z* (%): 399 (400, 401) $[MH]^+$ (100), 363 $[M - Cl]^+$ (30). Found (%): C, 57.42; H, 5.19; Cl, 17.37. Calc. for $C_{19}H_{20}Cl_2O_5$ (%): C, 57.16; H, 5.05; Cl, 17.76.

2-Allyl-2,4-dichloro-5-(2,3,4-trimethoxyphenyl)cyclopent-4-ene-1,3-dione **2b** prepared similarly from **1a** (0.1 g, 0.35 mmol) and 1,2,3-trimethoxybenzene (59 mg, 0.35 mmol). Yield 70 mg (54%). Dark yellow oil. IR (ν/cm^{-1}): 2998, 2941, 2905, 2837, 1761, 1723, 1597, 1496, 1479, 1465, 1435, 1414, 1319, 1298, 1256, 1233, 1187, 1174, 1073, 1035, 1009, 803, 777, 733, 695. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.94 (d, 2H, CH_2, *J* 7.5 Hz), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.19 (m, 2H, =CH_2), 5.61 (ddd, 1 H, =CH, *J* 7.3, 9.9 and 17.2 Hz), 6.77 (d, 1H, H-Ar, *J* 8.7 Hz), 7.05 (d, 1H, H-Ar, *J* 8.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.5 (CH_2), 56.2 (OCH_3), 56.4 (OCH_3), 60.8 (OCH_3), 61.3 (C^2), 107.1 and 125.2 (C^5_{Ar}, C^6_{Ar}), 113.1 (C^1_{Ar}), 122.3 (=CH_2), 128.7 (=CH), 138.1 (C^4), 142.0 (C^5), 149.1 (C_{Ar}), 152.3 (C_{Ar}), 152.7 (C_{Ar}), 189.6 (C=O), 191.8 (C=O). MS (EI), *m/z* (%): 371 (372, 373) $[MH]^+$ (33), 335 (336, 337) $[M - Cl]^+$ (100). Found (%): C, 55.32; H, 4.25; Cl, 19.52. Calc. for $C_{17}H_{16}Cl_2O_5$ (%): C, 55.0; H, 4.34; Cl, 19.10.

2-Allyl-2,4,5-trichlorocyclopent-4-ene-1,3-dione **4** was obtained as a side product with **2b** in the reaction of **1a** with 1,2,3-trimethoxybenzene. Yield 6.6 mg (8%). Pale yellow oil. IR (ν/cm^{-1}): 2985, 2933, 1739, 1733, 1714, 1573, 1435, 1417, 1363, 1274, 1255, 1212, 1142, 1036, 992, 897, 824, 750, 674, 636. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.97 (d, 2H, CH_2, *J* 7.3 Hz), 5.22-5.26 (m, 2H, =CH_2), 5.49 (ddd, 1H, =CH, *J* 7.5, 9.6 and 17.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$)

δ: 39.0 (CH_2), 61.2 (C^2), 123.3 (=CH_2), 127.7 (=CH), 150.6 (C^4, C^5), 186.5 (C=O). Found (%): C, 40.43; H, 2.22; Cl, 44.77. Calc. for $C_8H_5Cl_3O_2$ (%): C, 40.12; H, 2.10; Cl, 44.41.

2,4-Dichloro-2-(2-methylbut-3-en-2-yl)-5-(2,3,4-trimethoxyphenyl)cyclopent-4-ene-1,3-dione **3b** prepared similarly to **2a** from **1b** (0.1 g, 0.32 mmol) and 1,2,3-trimethoxybenzene (53 mg, 0.32 mmol). Yield 65 mg (51%). Yellow oil. IR (ν/cm^{-1}): 2997, 2939, 2907, 2837, 1721, 1597, 1496, 1479, 1435, 1414, 1298, 1256, 1233, 1174, 1036, 1009, 803, 776, 732, 695. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.15 (dd, 2H, =CH_2, *J* 10.6 and 17.3 Hz), 5.95 (dd, 1 H, =CH, *J* 17.2 and 10.8 Hz), 6.76 (d, 1H, H-Ar, *J* 8.7 Hz), 7.04 (d, 1H, H-Ar, *J* 8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.2 (CH_3), 23.1 (CH_3), 43.8 ($\underline{C}Me_2$), 56.3 (OCH_3), 60.8 and 60.9 (OCH_3), 61.3 (C^2), 107.1 и 125.4 (C^5_{Ar}, C^6_{Ar}), 113.2 (C^1_{Ar}), 115.8 (=CH_2), 140.5 (=CH), 138.2 (C^4), 142.1 (C^5), 148.8 (C_{Ar}), 152.4 (C_{Ar}), 156.9 (C_{Ar}), 189.9 (C=O), 192.3 (C=O). MS (EI), *m/z* (%): 399 (400, 401) $[MH]^+$ (28), 363 (364, 364) $[M\text{-}Cl]^+$ (100). Found (%): C, 57.51; H, 5.15; Cl, 17.29. Calc. for $C_{19}H_{20}Cl_2O_5$ (%): C, 57.16; H, 5.05; Cl, 17.76.

2,4,5-Trichloro-2-(methylbut-3-en-2-yl)cyclopent-4-ene-1,3-dione **5** was obtained as a side product with **3b** in the reaction of **1b** with 1,2,3-trimethoxybenzene. Yield 8.5 mg (10%). Pale yellow oil. IR (ν/cm^{-1}): 2983, 2943, 1774, 1761, 1729, 1584, 1512, 1473, 1465, 1416, 1245, 1207, 1182, 1158, 1001, 937, 909, 882, 810, 731, 677, 652. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 6H, CH_3), 5.15 (dd, 2H, =CH_2, *J* 10.7 and 17.2 Hz), 5.69 (dd, 1H, =CH, *J* 10.7 and 17.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.3 (CH_3), 43.9 ($\underline{C}Me_2$), 68.7 (C^2), 117.1 (=CH_2), 139.4 (=CH), 150.0 (C^4, C^5), 186.8 (C=O). Found (%): C, 44.53; H, 3.45; Cl, 40.02. Calc. for $C_{10}H_9Cl_3O_2$ (%): C, 44.89; H, 3.39; Cl, 39.75.

2-Allyl-2,4-dichloro-5-(2,5-dimethoxyphenyl)cyclopent-4-ene-1,3-dione **2c** was prepared similarly to **2a** from **1a** (0.1 g, 0.35 mmol) and 1,4-dimethoxybenzene (48 mg, 0.35 mmol). Yield 0.1 g (84%). Yellow oil. IR (ν/cm^{-1}): 2944, 2914, 1764, 1723, 1582, 1498, 1495, 1464, 1443, 1416, 1325, 1298, 1271, 1225, 1182, 1154, 1119, 1044, 1021, 935, 840, 814, 727, 689, 634. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.93 (d, 2H, CH_2, *J* 7.4 Hz), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.19 (m, 2H, =CH_2), 5.61 (dqd, 1H, =CH, *J* 7.3, 10.0 and 17.2 Hz), 6.83 (d, 1H, H-Ar, *J* 3.0 Hz), 6.96 (d, 1H, H-Ar, *J* 9.1 Hz), 7.04 (dd, 1H, H-Ar, *J* 3.0 and 9.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.6 (CH_2), 55.9 (OCH_3), 56.2 (OCH_3), 61.3 (C^2), 112.9 и 115.3 (C^6_{Ar}, C^3_{Ar}), 116.2 (C^1_{Ar}), 118.4 (C^4_{Ar}), 122.2 (=CH_2), 128.7 (=CH), 150.2 (C^4), 152.4 (C^5), 151.6 (C^5_{Ar}), 153.3 (C^2_{Ar}), 189.7 (C=O), 191.5 (C=O). MS (EI), *m/z* (%): 341 (342, 343) $[MH]^+$ (50), 305 (306, 307) $[M\text{-}Cl]^+$ (100). Found (%): C, 56.70; H, 4.02; Cl, 21.03. Calc. for $C_{16}H_{18}Cl_2O_4$ (%): C, 56.32; H, 4.14; Cl, 20.78.

2,4-Dichloro-5-(2,5-dimethoxyphenyl)-2-(2-methylbut-3-en-2-yl)cyclopent-4-ene-1,3-dione **3c** was prepared similarly from **1b** (0.1 g, 0.32 mmol) and 1,4-dimethoxybenzene (44 mg, 0.32 mmol). Yield 80 mg (68%). Yellow oil. IR (ν/cm^{-1}): 2933, 2917, 1723, 1717, 1498, 1465, 1416, 1298, 1269, 1224, 1181, 1045, 1021, 825. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.15 (dd, 2 H, $=CH_2$, *J* 10.8 and 17.2 Hz), 5.92 (dd, 1H, =CH, *J* 10.8 and 17.2 Hz), 6.84 (d, 1H, H-Ar, *J* 2.9 Hz), 6.98 (s, 1H, H-Ar), 7.04 (d, 1H, H-Ar, *J* 2.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.3 (CH_3), 22.9 (CH_3), 43.9 ($\underline{C}Me_2$), 56.0 (OCH_3), 56.3 (OCH_3), 69.6 (C^2), 113.1 и 115.3 (C^6_{Ar}, C^3_{Ar}), 115.9 ($=CH_2$), 116.5 (C^1_{Ar}), 118.4 (C^4_{Ar}), 140.5 (=CH), 149.9 (C^4), 151.7 (C^5), 152.2 (C^5_{Ar}), 153.4 (C^2_{Ar}), 190.1 (C=O), 191.9 (C=O). MS (EI), *m/z* (%): 369 (370, 371) $[MH]^+$ (78), 333 (334, 335) $[M - Cl]^+$ (100). Found (%): C, 58.88; H, 4.79; Cl, 19.54. Calc. for $C_{18}H_{18}Cl_2O_4$ (%): C, 58.55; H, 4.91; Cl, 19.20.

2-Allyl-2,4-dichloro-5-(4-methoxyphenyl)cyclopent-4-ene-1,3-dione **2d** was prepared similarly from **1a** (0.1 g, 0.35 mmol) and anisole (38 mg, 0.35 mmol). Yield 65 mg (60%). Yellow oil. IR (ν/cm^{-1}): 3008, 2936, 2913, 2841, 1757, 1717, 1604, 1574, 1561, 1507, 1463, 1441, 1424, 1435, 1309, 1283, 1261, 1223, 1182, 1163, 1140, 1118, 1061, 1026, 936, 886, 836, 792, 756, 681, 639, 586. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.94 (d, 2H, CH_2, *J* 7.5 Hz), 3.89 (s, 3H, OCH_3), 5.18 (m, 2H, $=CH_2$), 5.57 (ddd, 1H, =CH, *J* 7.3, 9.9 and 17.3 Hz), 7.04 (d, 1H, H-Ar, *J* 8.9 Hz), 8.01 (d, 1H, H-Ar, *J* 8.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.4 (CH_2), 55.6 (OCH_3), 60.9 (C^2), 114.3 (C^3_{Ar}, C^5_{Ar}), 120.8 (C^1_{Ar}), 122.4 ($=CH_2$), 128.6 (=CH), 132.5 (C^2_{Ar}, C^6_{Ar}), 145.4 (C^4), 149.3 (C^5), 162.7 (C^4_{Ar}), 189.5 (C=O), 193.3 (C=O). MS (EI), *m/z* (%): 311 (312, 313) $[MH]^+$ (49), 279 (280) $[M - OCH_3]^+$ (100), 275 (276, 277) $[M - Cl]^+$ (27). Found (%): C, 58.12; H, 3.77; Cl, 22.36. Calc. for $C_{15}H_{12}Cl_2O_3$ (%): C, 57.90; H, 3.89; Cl, 22.79.

2-Allyl-2,4-dichloro-5-(4-chloro-2-hydroxyphenyl)cyclopent-4-ene-1,3-dione **2e** was prepared similarly from **1a** (0.1 g, 0.35 mmol) and 3-chlorophenol (45 mg, 0.35 mmol). Yield 30 mg (26%). Yellow oil. IR (ν/cm^{-1}): 3377, 1722, 1717, 1605, 1290, 1233, 1211, 1161, 1039, 915, 858. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.96 (d, 2H, CH_2, *J* 7.3 Hz), 5.22 (m, 2H, $=CH_2$), 5.33 (s, 1H, OH), 5.62 (m, 1H, =CH), 6.88 (d, 1H, H-Ar, *J* 8.6 Hz), 7.05 (d, 1H, H-Ar, *J* 2.3 Hz), 7.22 (s, 1H, H-Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.8 (CH_2), 77.2 (C^2), 114.5 (C^6_{Ar}), 117.5 (C^3_{Ar}), 118.2 (C^1_{Ar}), 122.8 ($=CH_2$), 128.3 (=CH), 131.7 (C^4_{Ar}), 131.9 (C^5_{Ar}), 134.3 (C^4), 136.2 (C^5), 158.4 (C^2_{Ar}), 189.6 (C=O), 191.2 (C=O). MS (EI), *m/z* (%): 331 (330, 329) $[MH]^+$ (100). Found (%): C, 52.51; H, 3.13; Cl, 31.06. Calc. for $C_{15}H_{11}Cl_3O_3$ (%): C, 52.13; H, 3.21; Cl, 30.77.