Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2022, **32**, 183–185

Mendeleev Communications

Cytotoxicity of novel cross-conjugated arylated cyclopentene-1,3-diones

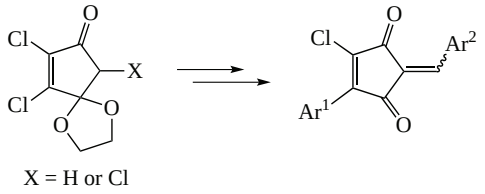
Victor A. Egorov,*[a] Lidiya S. Khasanova,[a] Fanuza A. Gimalova,*[a] Alexander N. Lobov,[a] Diana V. Ishmetova,[b] Vener A. Vakhitov[b] and Mansur S. Miftakhov[a]

[a] *Ufa Institute of Chemistry, Ufa Federal Research Center of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. E-mail: ammonika@mail.ru; fangim@anrb.ru*

[b] *Institute of Biochemistry and Genetics, Ufa Federal Research Center of the Russian Academy of Sciences, 450054 Ufa, Russian Federation*

DOI: 10.1016/j.mencom.2022.03.010

Novel 2,4-dichloro-5-phenylcyclopent-4-ene-1,3-dione and 5-aryl-4-chlorocyclopent-4-ene-1,3-dione were synthesized by the Suzuki–Miyaura or Friedel–Crafts reactions of the di- and trichlorocyclopentenone monoketals and subsequent hydrolysis of the ketal function. Condensation of these diones with (hetero)aromatic aldehydes afforded multifunctional 1,3-cyclopentenediones that showed anticancer activity.



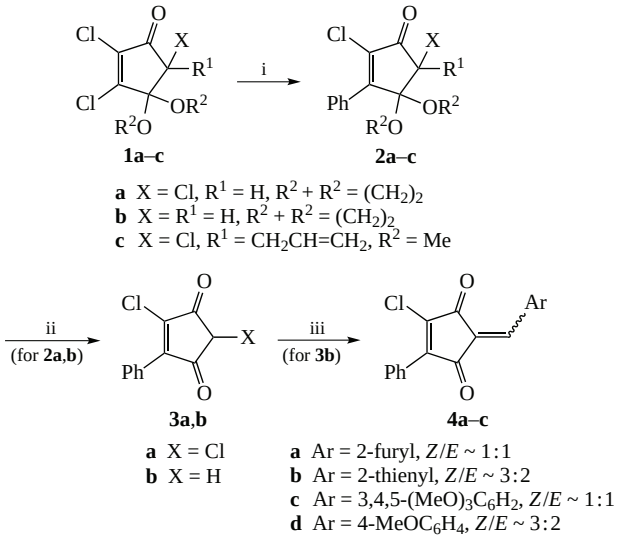
Keywords: organochlorine compounds, cyclopentenones, ketals, Suzuki–Miyaura reaction, Friedel–Crafts reaction, Knoevenagel condensation, aldehydes, cross-conjugated cyclopentene-1,3-diones, cytotoxicity.

Natural compounds and analogues comprising a system of cross-conjugated *exo*-alkylidenecyclopentene-1,3-dione[1–3] and *exo*-alkylidenecyclopentenone[4–6] show potent antifungal, antibacterial and anticancer properties. In this work, we planned to synthesize a new series of cross-conjugated cyclopentenediones using chlorocyclopentenones **1a**–**c**[7,8] as the starting materials (Scheme 1). The incorporation of a phenyl group into position C^5 was supposed to be performed by the Suzuki reaction[9–12] that is widely used in organic synthesis to create a C–C bond. A side methylidene substituent of aldol-crotonic type can be introduced by condensation with suitable aromatic and heteroaromatic aldehydes.

The Suzuki coupling[9] of chlorocyclopentenones **1a**,**b** with phenylboronic acid under standard conditions (dioxane–water, $Pd(PPh_3)_4$ catalyst, K_2CO_3)[13–15] gave 3-phenyl derivatives **2a**,**b** in 60–70% yields. The regioselectivity of the substitution of the 3-positioned chlorine atom in 2,3,5-trichlorocyclopentenone monoketals *vs.* C^2–Cl is attributed to its higher activity due to the electron-withdrawing effect of the keto group.[7] Removal of the ethylene ketal protective group in **2a**,**b** by treatment with conc. H_2SO_4 at 0 °C afforded diones **3a**,**b**. The presence of an allyl substituent in derivative **1c** complicates the reaction, and the yield of product **2c** is only 13% (see Scheme 1).

The C^2-functionalization variant that we developed for 4-chlorocyclopentenedione **3b** is shown in Scheme 1. Here, the condensation of lithiated dione **3b** (generated by its treatment with LDA in THF at –78 °C) with (hetero)aromatic aldehydes through intermediate aldols gave the target compounds **4a**–**d** as an inseparable mixture of *Z*,*E*-isomers. It can be seen that the structure of the resulting compounds comprises double cross-conjugation involving the carbonyls at C^1 and C^3.

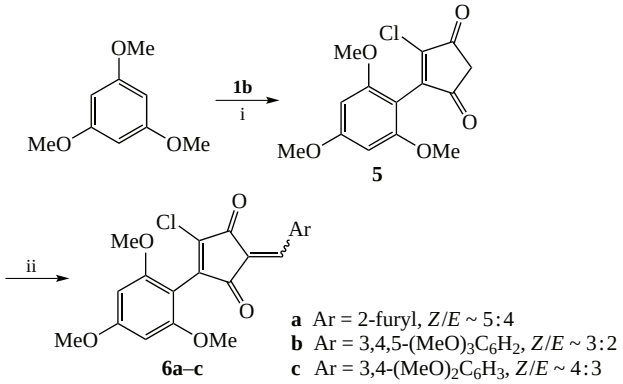
To study the effect of the nature of the aromatic substituent at C^5 on the cytotoxicity in comparison with dione **3b**, new cyclopentenedione **5** was synthesized by the previously developed method[16,17] *via* the Friedel–Crafts reaction (Scheme 2). Compound **5** was converted to derivatives **6a**–**c**



Scheme 1 *Reagents and conditions*: i, $PhB(OH)_2$, $Pd(PPh_3)_4$ (cat.), K_2CO_3, H_2O, dioxane, reflux; ii, H_2SO_4 (conc.), 0 °C, 1 h; iii, LDA, THF, –78 °C, then ArCHO.

The C^2-functionalization variant that we developed for 4-chlorocyclopentenedione **3b** is shown in Scheme 1. Here, the condensation of lithiated dione **3b** (generated by its treatment with LDA in THF at –78 °C) with (hetero)aromatic aldehydes through intermediate aldols gave the target compounds **4a**–**d** as an inseparable mixture of *Z*,*E*-isomers. It can be seen that the structure of the resulting compounds comprises double cross-conjugation involving the carbonyls at C^1 and C^3.

To study the effect of the nature of the aromatic substituent at C^5 on the cytotoxicity in comparison with dione **3b**, new cyclopentenedione **5** was synthesized by the previously developed method[16,17] *via* the Friedel–Crafts reaction (Scheme 2). Compound **5** was converted to derivatives **6a**–**c**



Scheme 2 *Reagents and conditions*: i, **1b**, $SnCl_4$, $C_2H_4Cl_2$, reflux; ii, LDA, THF, –78 °C, then ArCHO.

Table 1 *In vitro* cytotoxic activity of compounds **3b**, **4a–c** and **5**, **6a–c** against human HEK293, SH-SY5Y, HepG2, Jurkat, MCF-7 and A549 cell lines.[a]

Compound	IC_{50}/μM					
	HEK293	SH-SY5Y	HepG2	Jurkat	MCF-7	A549
3b	62.46 ± 2.91	17.43 ± 2.11 (p = 0.000009)	35.41 ± 3.53 (p = 0.000010)	22.89 ± 4.66 (p = 0.000009)	48.22 ± 1.83 (p = 0.0003)	85.91 ± 2.98 (p = 0.000011)
4a	35.54 ± 2.86	9.57 ± 0.67 (p = 0.000009)	14.68 ± 2.19 (p = 0.000009)	6.48 ± 1.39 (p = 0.000009)	14.07 ± 1.89 (p = 0.000009)	13.72 ± 1.07 (p = 0.000009)
4b	39.59 ± 3.54	10.27 ± 0.08 (p = 0.000009)	24.09 ± 1.88 (p = 0.000018)	9.84 ± 1.82 (p = 0.000009)	19.41 ± 1.55 (p = 0.000009)	57.45 ± 3.84 (p = 0.000011)
4c	35.27 ± 0.18	47.58 ± 0.85 (p = 0.000006)	23.40 ± 2.22 (p = 0.000007)	57.66 ± 1.47 (p = 0.00002)	32.40 ± 1.25	34.23 ± 0.52
5	11.75 ± 0.52	4.82 ± 0.06 (p = 0.000011)	15.33 ± 0.80 (p = 0.001)	5.03 ± 0.18 (p = 0.000011)	8.61 ± 1.34 (p = 0.003)	18.26 ± 1.31 (p = 0.000012)
6a	10.42 ± 1.09	2.90 ± 0.05 (p = 0.00001)	7.01 ± 1.98 (p = 0.003)	4.95 ± 0.29 (p = 0.00005)	8.17 ± 0.10 (p = 0.04)	11.47 ± 0.72 (p = 0.5)
6b	15.96 ± 0.41	27.04 ± 2.97 (p = 0.00001)	22.52 ± 0.27 (p = 0.0006)	7.49 ± 0.23 (p = 0.00002)	10.75 ± 0.04 (p = 0.003)	10.54 ± 0.58 (p = 0.002)
6c	11.43 ± 0.24	19.00 ± 2.84 (p = 0.004)	12.62 ± 0.11	22.56 ± 0.48 (p = 0.00001)	34.15 ± 3.69 (p = 0.000006)	16.29 ± 0.36
Fluorouracil	7.43 ± 0.83	1.97 ± 0.4	1.83 ± 0.2	0.70 ± 0.10	1.20 ± 0.09	0.32 ± 0.02

[a] Data are presented as the mean values ±SD from two independent experiments performed in triplicate. The p-value indicates a comparison of IC_{50} values for SH-SY5Y, HepG2, Jurkat, MCF-7 and A549 with IC_{50} values for HEK293 cells (one-way ANOVA with Dunnett's post-hoc test).

using the corresponding aldehydes, similarly to compounds **4a–d** (see Scheme 1).

The structures of compounds **4a**,**b** and **6a**,**b** were determined from the ^{1}H, ^{13}C NMR spectra using two-dimensional correlation {^{1}H, ^{13}C} HSQC, HMBC and LR-HSQMBC, as well as {^{1}H, ^{1}H} dqCOSY and NOESY. Based on the spectral data obtained, it was found that the reaction products consisted of a mixture of *E*- and *Z*-isomers of 4-chloro-2-arylidene-5-arylcyclopent-4-ene-1,3-diones where the latter was slightly predominant. The assignment of the *Z*- and *E*-isomers was based on the carbon–hydrogen coupling constants with calculations from the LR-HSQMBC spectra and was confirmed by B3LYP/6-311++G(d,p)u+1 [for details, see Online Supplementary Materials, Figure S11(*a*),(*b*) and Table S1]. The LR-HSQMBC experiment developed by Williamson *et al.*[18] was optimized to observe the entire range of weak long-distance $^nJ_{CH}$ correlations and gave intense well-resolved cross-peaks.[19,20]

Data on the cytotoxicity of compounds **3b**, **4a–c** and **5**, **6a–c** are given in Table 1. The tested compounds exhibit a cytotoxic effect in all the cell lines with pronounced activity, mainly against SH-SY5Y neuroblastoma cells and Jurkat T-lymphoblastic leukemia cells (with IC_{50} values <10 μM for compounds **4a**,**c**, **5**, **6a**,**b**). Compound **6a** also showed pronounced activity against human hepatocellular carcinoma cells HepG2 (IC_{50} 7.01 μM). The A549 lung carcinoma cell line was found to be less sensitive to the effect of compounds **3b** and **4b**, whereas compounds **4a**, **5** and **6a** exhibited moderate activity.

It is noteworthy that dione **6a** showed the strongest activity among this series of compounds toward all the cell lines and was 2–5 times more active than compound **4a**. Apparently, this is due to the fact that, in comparison with the phenyl group of compounds **4a** and **4b**, the trimethoxyphenyl moiety in **6a** is more electron-saturated, which is also observed in the pairs of **4c** and **6b**.

The furan-containing cyclopentenone **4a** exhibited a significantly higher cytotoxicity than ω-thiophene-containing **4b** (see Table 1). Here, like in the pair of **3b** and **5**, we attribute the differences in cytotoxicity to the differences in the electron-donating ability of aromatic and heteroaromatic substituents in cyclopentenediones.

To conclude, using chlorocyclopentenones as an example, we have demonstrated that it is possible to use the Suzuki and Friedel–Crafts reactions for the regioselective arylation of vicinal 2,3-dichlorocyclopentenones, which provided synthesis of pharmacologically promising cross-conjugated cyclopentenediones.

This study was supported by state assignments nos. AAAA-A20-120012090021-4 and AAAA-A20-120012090029-0. The spectral and analytical studies were performed using the equipment of the *Khimiya* Joint Center, Ufa Institute of Chemistry of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.010.

References

1 X.-C. Li, D. Ferreira, M. R. Jacob, Q. Zhang, S. I. Khan, H. N. ElSohly, D. G. Nagle, T. J. Smillie, I. K. Khan, L. A. Walker and A. M. Clark, *J. Am. Chem. Soc*., 2004, **126**, 6872.
2 H. Hori, H. Nagasawa, M. Ishibashi, Y. Uto, A. Hirata, K. Saijo, K. Ohkura, K. L. Kirk and Y. Uehara, *Bioorg. Med. Chem*., 2002, **10**, 3257.
3 S. K. Babu, X.-C. Li, M. R. Jacob, Q. Zhang, S. I. Khan, D. Ferreira and A. M. Clark, *J. Med. Chem.*, 2006, **49**, 7877.
4 D. S. Straus and C. K. Glass, *Med. Res. Rev.*, 2001, **21**, 185.
5 V. V. Loza, A. M. Gimazetdinov and M. S. Miftakhov, *Russ. J. Org. Chem.*, 2018, **54**, 1585 (*Zh. Org. Khim*., 2018, **54**, 1575).
6 Y. Takahashi, H. Kosugi and H. Uda, *J. Chem. Soc., Chem. Commun*., 1982, 496.
7 R. R. Akhmetvaleev, F. A. Akbutina, N. A. Ivanova and M. S. Miftakhov, *Russ. Chem. Bull*., 2001, **50**, 1489 (*Izv. Akad. Nauk, Ser. Khim*., 2001, 1417).
8 O. M. Kuznetsov, R. R. Akhmetvaleev, N. S. Vostrikov and M. S. Miftakhov, *Russ. Chem. Bull.*, 1996, **45**, 982 (*Izv. Akad. Nauk, Ser. Khim*., 1996, 1027).
9 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) A. Suzuki, *Angew. Chem., Int. Ed*., 2011, **50**, 6723; (*c*) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147; (*d*) F. Bellina, A. Carpita and R. Rossi, *Synthesis*, 2004, **15**, 2419.
10 A. A. Vasil'ev, A. S. Burukin, G. M. Zhdankina and S. G. Zlotin, *Mendeleev Commun.*, 2021, **31**, 400.
11 E. S. Matyugina, A. L. Khandazhinskaya, S. N. Kochetkov and K. L. Seley-Radtke, *Mendeleev Commun.*, 2020, **30**, 231.
12 E. V. Nosova, T. N. Moshkina, G. N. Lipunova, I. V. Baklanova, D. S. Kopchuk, P. A. Slepukhin and V. N. Charushin, *Mendeleev Commun.*, 2018, **28**, 14.

13 R. A. Khera, M. Hussain, N. T. Hung, N. Eleya, H. Feist, A. Villinger and P. Langer, *Helv. Chim. Acta*, 2012, **95**, 469.
14 M. Hussain, N. T. Hung, N. Eleya, H. Feist, A. Villinger and P. Langer, *Tetrahedron Lett.*, 2011, **52**, 184.
15 D. S. Zinad, M. Hussain, N. T. Hung and A. Langer, *Eur. J. Org. Chem.*, 2011, **22**, 4212.
16 V. A. Egorov, F. A. Gimalova, Z. R. Zileeva, L. F. Zainullina, Yu. V. Vakhitova and M. S. Miftakhov, *Mendeleev Commun.*, 2019, **29**, 174.
17 V. A. Egorov, L. M. Khalilov, E. S. Mescheryakova, F. A. Gimalova and M. S. Miftakhov, *Russ. Chem. Bull*., 2021, **70**, 128.
18 R. T. Williamson, A. V. Buevich, G. E. Martin and T. Parella, *J. Org. Chem*., 2014, **79**, 3887.
19 P. Bigler and J. Furrer, *Magn. Reson. Chem*., 2018, **56**, 1101.
20 P. Bigler and J. Furrer, *Magn. Reson. Chem.*, 2019, **57**, 129.

Received: 9th September 2021; Com. 21/6687