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SHORT COMMUNICATIONS

Synthesis of Chloramphenicol Conjugate with Fullerene C_{60}

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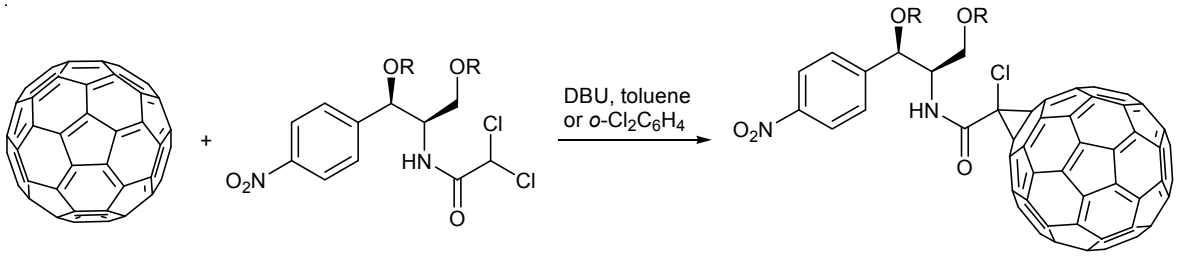
Main efforts in the design and synthesis of organofunctionalized derivatives of fullerene C_{60} for medical purposes are addressed to create water-soluble compounds [1–3]. Among them, antiviral [4], anticarcinogenic [5], and antibacterial agents [6], radical scavengers [7], etc. [8], have been found. An important research line in this field is the synthesis of coordination and covalently bound C_{60} compounds with biologically active molecules used in medical practice. For example, the anticancer activity of the C_{60}–doxorubicin complex is higher by a factor of 1.5–2 than the activity of doxorubicin taken alone [9]; analogous effect is observed for the complex C_{60}–dexamethasone [10]. As a rule, the complexation improves transport and prolongs action of drugs, and in some cases synergistic effect is achieved.

A different situation is observed with covalent bonding of C_{60} with drugs. Zakharian et al. [11] proposed to use C_{60} conjugate with paclitaxel (Taxol) for lipophilic chemotherapy of lung cancer. It was noted that C_{60} is an ideal partner for the lipophilization of drugs via conjugation. Conjugates of C_{60} with antibiotics [12] have been patented, and C_{60} conjugates with isoniazid [13], dehydroabietylamine [14], amino acids [15], and other biologically active molecules have been synthesized. In most cases, the biological activity profile was retained; however, it may change since a radically new molecular architecture is concerned.

In the antibiotics series, an exceptionally important problem is pathogen resistance to drugs [16]; therefore, either modification of known antibiotics or design of compounds with novel mechanisms of action is necessary. In this work we made an attempt to synthesize C_{60} conjugate with a broad-spectrum antibiotic, chloramphenicol (**1**). Molecule **1** contains a dichloromethyl group which should be active in the Bingel cyclopropanation of C_{60} [17, 18]. In fact, compound **1** smoothly reacted with C_{60} in *o*-dichlorobenzene in the presence of 2–3 equiv of DBU to give 20% of adduct **2**. Compound **2** is soluble in technological solvents, including DMSO.

The cyclopropanation of C_{60} with diacetate **3** was carried out under analogous conditions. The product, methanofullerene **4**, was soluble in chloroform and toluene, but its solubility in DMSO was lower than that of adduct **2**. Diacetate **4** and diol **2** may be regarded as new potential biologically active compounds and prodrugs since acetates and amides are known to readily undergo *in vivo* hydrolysis to alcohols and amines, respectively.



1, **3** **2**, **4**

1, **2**, R = H; **3**, **4**, R = Ac.

(1*R*,2*R*)-2-{[3′-Chloro-3′*H*-cyclopropa[1,9]-(C_{60}-I_h)[5,6]fulleren-3′-yl]carbonylamino}-3-hydroxy-1-(4-nitrophenyl)propan-1-ol (2). Fullerene C_{60}, 0.1 g (0.138 mmol), was dissolved in 20 mL of *o*-dichlorobenzene, 0.053 g (0.166 mmol) of chloramphenicol (**1**) and 0.053 g (0.414 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were added, and the mixture was stirred for 24 h at room temperature (TLC). The solvent was distilled off under reduced pressure, and the product was isolated by silica gel column chromatography (methylene chloride–methanol, 100:1). Yield 0.04 g (30%), dark brown powder. IR spectrum, ν, cm^{-1}: 3323, 2360, 1688, 1517, 1348, 1224, 1048, 749, 530. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.80 br.s (2H, CH_2O), 4.20 br.s (1H, CHO), 5.25 s (1H, CHN), 5.80 s (1H, NH), 7.50 d (2H, H_{arom}, J = 8.6 Hz), 8.20 d (2H, H_{arom}, J = 8.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 55.65 (CHNH), 60.01 (C_{sp^3} in C_{60}), 63.10 (CH_2OH), 68.0 (CCl), 72.39 (CHOH); 122.75, 127.43 (C_{arom}); 133.00, 133.45, 135.20, 142.40, 144.76, 150.34, 170.21 (C=O). Mass spectrum: *m*/*z* 1006.068 $[M]^+$. $C_{71}H_{11}ClN_2O_5$. Calculated: *M* 1006.035.

In addition, 0.04 g of unreacted C_{60} (mp >350°C) was isolated.

(1*R*,2*R*)-3-Acetoxy-2-[(dichloroacetyl)amino]-1-(4-nitrophenyl)propyl acetate (3). A solution of 0.2 g (0.62 mmol) of compound **1** in 0.5 mL (6.2 mmol) of pyridine was cooled to 0°C, 0.31 mL (3.1 mmol) of acetic anhydride was added dropwise, and the mixture was stirred for 6 h at room temperature (TLC). The mixture was washed with brine and extracted with chloroform. The organic phase was separated, dried over $MgSO_4$, and evaporated, and the residue was purified by silica gel column chromatography (petroleum ether–ethyl acetate, 1:1). Yield 0.22 g (91%), amorphous solid, mp 140°C. IR spectrum, ν, cm^{-1}: 3318, 1745, 1686, 1520, 1350, 1064, 844, 656. ^1H NMR spectrum, δ, ppm: 2.10 s (3H, CH_3), 2.20 s (3H, CH_3), 4.08 d.d (1H, J = 6.1, 11.7 Hz) and 4.18 d.d (1H, J = 5.2, 11.7 Hz) (CH_2O), 4.60 sext (1H, C**H**NH, J = 5.6 Hz), 5.85 s (1H, $CHCl_2$), 6.08 d (1H, CHO, J = 5.7 Hz), 6.75 d (1H, NH, J = 9.4 Hz), 7.52 d.d (2H, H_{arom}, J = 1.8, 6.8 Hz), 8.22 d.d (2H, H_{arom}, J = 1.9, 6.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.63 (CH_3), 20.81 (CH_3), 60.38 (CHN), 62.18 (CH_2O), 66.03 ($CHCl_2$), 72.72 (CHO); 124.04, 127.60, 143.30, 148.18 (C_{arom}); 164.18 (CONH), 169.59 (C=O), 170.47 (C=O).

(1*R*,2*R*)-3-Acetoxy-2-{[3′-chloro-3′*H*-cyclopropa-[1,9](C_{60}-I_h)[5,6]fulleren-3′-yl]carbonylamino}-1-(4-nitrophenyl)propyl acetate (4). Fullerene C_{60}, 0.1 g (0.138 mmol), was dissolved in 30 mL of toluene, 0.065 g (0.166 mmol) of compound **3** and 0.062 g (0.414 mmol) of DBU were added, and the mixture was stirred for 24 h at room temperature (TLC). The mixture was evaporated, and the product was isolated by silica gel column chromatography (toluene, methylene chloride). Yield 0.06 g (40%), dark brown powder. IR spectrum, ν, cm^{-1}: 3318, 1745, 1681, 1522, 1349, 1224, 1051, 811, 530. ^1H NMR spectrum, δ, ppm**:** 2.15 s (3H, CH_3), 2.30 s (3H, CH_3), 4.23 d.d (1H, CH_2O, J = 6.5, 11.8 Hz), 4.40 d.d (1H, CH_2O, J = 6.4, 11.6 Hz), 4.97 sext (1H, C**H**NH, J = 5.6 Hz), 6.25 d (1H, CHO, J = 4.7 Hz), 7.18 d (1H, NH, J = 9.0 Hz), 7.63 d (2H, H_{arom}, J = 8.6 Hz), 8.25 d (1H, H_{arom}, J = 8.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.80 (CH_3), 21.00 (CH_3), 62.58 (CH_2O), 67.09 (CHN), 72.90 (CHO); 124.18, 127.37, 143.88, 148.00 (C_{arom}); 139.00, 139.20, 141.13 (2C), 142.19, 143.03, 143.10, 143.15, 143.47, 143.69, 144.07, 144.19, 144.51, 144.80 (2C), 144.86, 145.22, 145.31, 145.37 (C_{60}), 163.08 (CONH), 169.67 (C=O), 170.07 (C=O). Mass spectrum: *m*/*z* 1090.076 $[M]^+$. $C_{75}H_{15}ClN_2O_7$. Calculated: *M* 1090.056.

In addition, 0.03 g of unreacted C_{60} (mp >350°C) was isolated.

The IR spectra were recorded on a Shimadzu IR Prestige-21 spectrometer from films. The ^1H NMR spectra were measured on a Bruker AM-300 spectrometer at 300.13 MHz using $CDCl_3$ as solvent and tetramethylsilane as internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance-500 instrument at 125.77 MHz. The mass spectra (MALDI) were obtained on a Voyager-DE STR MALDI TOF mass spectrometer. The progress of reactions was monitored by TLC on Sorbfil plates (Russia); spots were detected by calcination or treatment with an alkaline solution of potassium permanganate. Column chromatography was performed using 30–60 g of silica gel per gram of substrate; freshly distilled solvents were used for elution.

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REFERENCES

1. Nakamura, E. and Isobe, H., *Acc. Chem. Res.*, 2003, vol. 36, p. 807.
2. Nierengarten, I. and Nierengarten, J.-F., *Chem. – Asian J.*, 2014, vol. 9, no. 6, p. 1436.

3. Wang, J., Zrang, Zh., Wu, W., and Jiang, X., *Chin. J. Chem*., 2014, vol. 32, no. 1, p. 78.
4. Kornev, A.B., Peregudov, A.S., Martynenko, V.M., Balzarini, J., Hoovelbeke, B., and Troshin, P.A., *Chem. Commun*., 2011, vol. 47, p. 8298.
5. Ikeda, A., Hatano, H., Kawaguchi, M., Suenaga, H., and Shinkai, S., *Chem. Commun*., 1999, p. 1403.
6. Durka, M., Buffet, K., Iehl, J., Holler, M., Nierengarten, J.-F., Taganna, J., Bouckaert, J., and Vincent, S.P., *Chem. Commun*., 2011, vol. 47, p. 1321.
7. Wolff, D.J., Mialkowski, K., Richardson, C.F., and Wilson, S.R., *Biochemistry*, 2001, vol. 40, p. 37.
8. Xia, L., Takada, H., Maed, K., Haramoto, M., and Miwa, N., *Biomed. Pharmacother*., 2005, vol. 59, p. 351.
9. Panchuk, R.R., Prylutska, S.V., Chumak, V.V., Skorochodov, N.R., Lehka, L.V., Evstigneev, M.P., Prylutskyy, Yu.L., Berger, W., Heffeter, P., Scharff, P., Ritter, U., and Stoika, R.S., *J. Biomed. Nanotechnol*., 2015, vol. 11, p. 1139.
10. Liu, R., Cai, X., Wang, J., Li, J., Huang, Q., and Li, W., *J. Nanosci. Nanotechnol*., 2009, vol. 9, no. 5, p. 3171.
11. Zakharian, T.Y., Seryshev, A., Sitharaman, B., Gilbert, B.E., Knight, V., and Wilson, L.J., *J. Am. Chem. Soc*., 2005, vol. 127, p. 12508.
12. Wilson, L.J., Mirakyan, A.L., and Cubbade, M.P., US Patent no. 20040241173 A1, 2004.
13. Kumar, A., Patel, G., and Menon, S.-K. *Chem. Biol. Drug Des*., 2009, vol. 73, no. 5, p. 553.
14. Zhou, Z., Lin, Z.-X. , Liang, D., and Hu, J.-Q., *Tetrahedron*, 2003, vol. 69, p. 43.
15. Andreev, S.M., Babakhin, A.A., Petrukhina, A.O., Romanova, V.S., Parnes, Z.N., and Petrov, R.V., *Dokl. Akad. Nauk*, 2000, vol. 370, no. 2, p. 261.
16. Rossi, F., *Clin. Infect. Dis*., 2011, vol. 52, p. 1138.
17. Bingel, C., *Chem. Ber*., 1993, vol. 126, p. 1957.
18. Torosyan, S.A., Gimalova, F.A., Biglova, Yu.N., Mikheev, V.V., and Miftakhov, M.S., *Russ. J. Org. Chem*., 2012, vol. 48, p. 736.