Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2017, **27**, 608–609

Mendeleev Communications

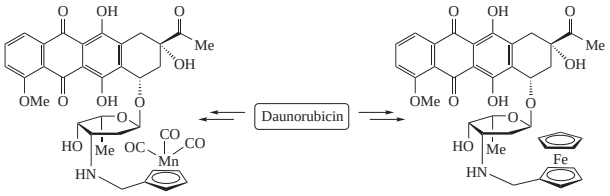
Synthesis of hybrid compounds composed of daunorubicin covalently linked with Cp_2Fe and $CpMn(CO)_3$

Elena V. Sharova, Oleg I. Artyushin, Natalya V. Vinogradova, Galina K. Genkina and Valery K. Brel*

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 6373; e-mail: v_brel@mail.ru

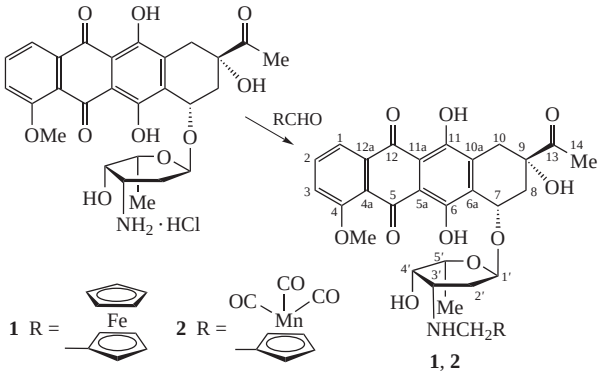
DOI: 10.1016/j.mencom.2017.11.023

Hybrid molecules wherein five-membered rings of ferrocene or cymanthrene are covalently bonded with the amino group of daunorubicin through a methylene linker, have been synthesized by reductive amination of the corresponding aldehydes [M]C_5H_4CHO {[M] = CpFe or $(CO)_3$Mn} using daunorubicin as an amine component.



Recently, a novel trend in organometallic chemistry, namely, bioorganometallic chemistry, has attracted a greater attention,[1] since novel classes of organometallic compounds were found to play a key role in biochemical and biological processes.[2] The main strategy in design of the biologically active organometallic compounds is based on constructing hybrid molecular systems that comprise an organometallic unit covalently bonded to a biologically active organic molecule.[3] Introduction of organometallic moieties into various physiologically active compounds often results in a rise of the biological activity and extension of a pharmacological profile of an organic substrate.[4] Among organometallic compounds including metallocene ones, of special interest are ferrocene and cymanthrene derivatives possessing pronounced antiproliferative properties.[1(a),5] However, their covalent conjugates with antitumor anthracycline antibiotics were not reported although chemical modification of the anthracyclines has been studied for a rather long time. Examples of their acylation,[6] alkylation,[7] trimethylsilylation,[8] introduction of fluorinated substituents[9] or phosphorus-containing groups[10] were described.

In the present work, we have accomplished a synthesis of hybrid molecules **1**, **2** containing daunorubicin and ferrocene or cymanthrene moiety (Scheme 1). In compounds **1**, **2**, cyclopentadiene rings are covalently bonded through methylene linkers with an amino group of the carbohydrate fragment of daunorubicin.



Scheme 1 *Reagents and conditions*: $NaBH_3(CN)$, MeCN, H_2O, room temperature, darkness.

To access conjugates **1**, **2**, we applied the reductive amination method[11] to ferrocenecarbaldehyde or cymanthrenecarbaldehyde using daunorubicin as an amine component. The reaction was performed in aqueous acetonitrile; imines formed at the first step were reduced with sodium borohydride without isolation. Final products **1**, **2** were isolated using column chromatography on silica gel in 60% yield. The structures of compounds **1**, **2** were confirmed by the ^{1}H and ^{13}C NMR spectroscopy.†

† Daunorubicin hydrochloride was purchased from Aldrich. Ferrocenecarbaldehyde[12] and cymanthrenecarbaldehyde were synthesized using the known methods. Atom numbering in compounds **1**, **2** is given according to Tong *et al.*[13]

Conjugates **1**, **2**. A mixture of a metallocenecarbaldehyde (8.0 mmol) and daunorubicin hydrochloride (225 mg, 0.4 mmol) in acetonitrile–H_2O (3 : 1, 9 ml) was stirred at room temperature in the darkness for 0.5 h. Then, $NaBH_3(CN)$ (76 mg, 1.2 mmol) was added and stirring was continued for 0.5 h. The mixture was quenched with H_2O (5 ml) and extracted with $CHCl_3$ (3 × 10 ml). The organic layers were washed with H_2O (15 ml) and water layers were re-extracted with $CHCl_3$ (15 ml). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel.

N-*(Ferrocenylmethyl)daunorubicin* **1**. Eluent, $CHCl_3$–MeOH (50 : 3), red powder, yield 58%. IR (KBr, ν/cm^{-1}): 3449 (OH + NH), 3091 (CH), 2933 (CH), 2851 (CH), 1716 (C=O), 1617, 1579, 1445, 1413, 1383, 1352, 1285, 1233, 1210, 1119, 1107, 1088, 1070, 1034, 989, 816, 764, 484. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 14.07 (br. s, 1H, 6-OH), 13.25 (br. s, 1H, 11-OH), 8.07 (d, 1H, 1-H, $^3J_{HH}$ 7.2 Hz), 7.81 (t, 1H, 2-H, $^3J_{HH}$ 7.8 Hz), 7.42 (t, 1H, 3-H, $^3J_{HH}$ 8.0 Hz), 5.55 (br. s, 1H, 1′-H), 5.29 (br. s, 1H, 7-H), 4.33 (s, 2H, $^1/_2C_5H_4$), 4.11 (br. s, 7H, C_5H_5 + $^1/_2C_5H_4$), 4.08 (s, 3H, 4-OMe), 3.95 and 3.84 (2s, 2H, NCH_2), 3.80–3.65 (m, 2H, 5′-H, 4′-H), 3.15–2.95 (m, 1H, 3′-H), 3.24 (d, 1H, 10-H_A, $^2J_{HH}$ 20.0 Hz), 2.96 (d, 1H, 10-H_B, $^2J_{HH}$ 20.0 Hz), 2.43 (s, 3H, 14-Me), 2.34 (d, 1H, 8-H_A, $^2J_{HH}$ 12.0 Hz), 2.10 (d, 1H, 8-H_B, $^2J_{HH}$ 12.0 Hz), 2.15–1.80 (m, 4H, 11-OH + 6-OH + 2′-H), 1.34 (d, 3H, 5′-Me, $^3J_{HH}$ 8.0 Hz). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 211.79 (C^{13}), 186.95 (C^{12}), 186.61 (C^5), 160.98 (C^4), 156.31 (C^6), 155.79 (C^{11}), 135.69 (C^3), 135.41 (C^{12a}), 134.45 (C^{6a}), 134.09 (C^{4a}), 120.80 (C^{10a}), 119.71 (C^2), 118.35 (C^1), 111.30 (C^{11a}), 111.16 (C^{5a}), 100.31 ($C^{1'}$), 76.59 (*ipso*-C_5H_4), 68.50 (unsubstituted C_5H_5), 69.28, 68.87, 66.98 and 66.36 (C_5H_4 in Fc), 56.58 (C^7), 52.01 ($C^{5'}$), 44.40 (NCH_2), 34.89 (C^{10}), 33.19 (C^8), 24.71 (14-Me), 16.79 (5′-Me). Found (%): C, 60.48; H, 4.82; N, 1.81; Fe, 6.90. Calc. for $3C_{38}H_{39}O_{10}NFe \cdot 2CH_2Cl_2$ (%): C, 59.37; H, 5.20; N, 1.79; Fe, 7.14. MS (MALDI-TOF), *m*/*z*: 725.19 $[M]^+$.

In summary, the synthesis of hybrid molecules from ferrocenecarbaldehyde or cymanthrenecarbaldehyde and antitumor anthracycline antibiotic, daunorubicin, has been performed in good yields. The reductive amination provides an approach to bioconjugates wherein daunorubicin is covalently bonded through a methylene spacer with Cp_2Fe or $CpMn(CO)_3$ moiety.

This work was supported by the Russian Foundation for Basic Research (project no. 15-03-00663).

References

1 (*a*) D. R. van Staveren and N. Metzler-Nolte, *Chem. Rev.*, 2004, **104**, 5931; (*b*) C. G. Hartinger and P. J. Dyson, *Chem. Soc. Rev.*, 2009, **38**, 391.
2 (*a*) M. Patra, G. Gasser and N. Metzler-Nolte, *Dalton Trans.*, 2012, **41**, 6350; (*b*) M. Patra and G. Gasser, *ChemBioChem*, 2012, **13**, 1232.
3 *Bioorganometallics*, ed. G. Jaouen, Wiley-VCH, Weinheim, 2006.
4 (*a*) L. V. Snegur, Yu. S. Nekrasov, N. S. Sergeeva, Z. V. Zhilina, V. V. Gumenyuk, Z. A. Starikova, A. A. Simenel, N. B. Morozova, I. K. Sviridova and V. N. Babin, *Appl. Organomet. Chem.*, 2008, **22**, 139; (*b*) S. Z. Vatsadze, D. A. Shulga, Yu. D. Loginova, I. A. Vatsadze, L. Wang, H. Yu and K. V. Kudryavtsev, *Mendeleev Commun.*, 2016, **26**, 212.

N-*(Cymanthrenylmethyl)daunorubicin* **2**. Eluent, $CHCl_3$–MeOH (50 : 1), red powder, yield 64%. IR (KBr, ν/cm^{-1}): 3482 (OH + NH), 3102 (CH), 2973 (CH), 2935 (CH), 2844 (CH), 2017 [very strong C≡O(A1)], 1920 [very strong C≡O(E)], 1716 (C=O), 1617, 1578, 1445, 1413, 1379, 1352, 1286, 1261, 1232, 1209, 1121, 1107, 1083, 1069, 1034, 985, 952, 819, 764, 669, 636, 540, 463. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 14.00 (s, 1H, 6-OH), 13.30 (s, 1H, 11-OH), 8.04 (d, 1H, 1-H, $^3J_{HH}$ 7.2 Hz), 7.80 (t, 1H, 2-H, $^3J_{HH}$ 8.0 Hz), 7.41 (d, 1H, 3-H, $^3J_{HH}$ 8.0 Hz), 5.54 (br. s, 1H, 1′-H), 5.32 (br. s, 1H, 7-H), 4.76 and 4.72 (2s, 2H, NCH_2), 4.67 (s, 3H, 4-OMe), 4.11 (s, 4H, C_5H_4), 3.65 (br. s, 1H, 5′-H), 3.46 (br. s, 1H, 4′-H), 3.37 (br. s, 1H, 3′-H), 3.24 (d, 1H, 10-H_A, $^2J_{HH}$ 18.8 Hz), 2.96 (d, 1H, 10-H_B, $^2J_{HH}$ 18.4 Hz), 2.44 (s, 3H, 14-Me), 2.38 (br. d, 1H, 8-H_A, $^2J_{HH}$ 12.0 Hz), 2.13 (br. d, 1H, 8-H_B, $^2J_{HH}$ 12.0 Hz), 1.74 (br. s, 5H, 11-OH, 6-OH, NH, 2′-H), 1.40 (br. s, 3H, 5′-Me). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 224.59 (CO), 211.64 (C^{13}), 186.97 (C^{12}), 186.61 (C^5), 160.96 (C^4), 156.31 (C^6), 157.77 (C^{11}), 135.61 (C^3), 135.43 (C^{12a}), 134.31 (C^{6a}), 134.10 (C^{4a}), 120.84 (C^{10a}), 119.70 (C^2), 118.31 (C^1), 111.34 (C^{11a}), 111.19 (C^{5a}), 100.70 ($C^{1'}$), 82.35, 82.12 and 81.61 (C_5H_4), 69.71 (C^9), 56.58 (C^7), 34.81 (C^{10}), 33.28 (C^8), 24.67 (14-Me), 16.98 (5′-Me). Found (%): C, 58.21; H, 4.44; N, 1.84; Mn, 7.60. Calc. for $C_{36}H_{38}O_{13}NMn$ (%): C, 57.83; H, 5.12; N, 1.87; Mn, 7.35. MS (MALDI-TOF), *m*/*z*: 606.22 [M – $Mn(CO)_3$]$^+$.

5 (*a*) E. Meggers, G. E. Atilla-Gokcumen, H. Bregman, J. Maksimoska, S. P. Mulcahy, N. Pagano and D. S. Williams, *Synlett*, 2007, 1177; (*b*) D. S. Williams, G. E. Atilla, H. Bregman, A. Arzoumanian, P. S. Klein and E. Meggers, *Angew. Chem. Int. Ed.*, 2005, **44**, 1984; (*c*) C. Policar, J. B. Waern, M.-A. Plamont, S. Clède, C. Mayet, R. Prazeres, J.-M. Ortega, A. Vessières and A. Dazzi, *Angew. Chem. Int. Ed.*, 2011, **50**, 860; (*d*) H. W. P. N'Dongo, I. Neundorf, K. Merz and U. Schatzschneider, *J. Inorg. Biochem.*, 2008, **102**, 2114; (*e*) I. Neundorf, J. Hoyer, K. Splith, R. Rennert, H. W. P. N'Dongo and U. Schatzschneider, *Chem. Commun.*, 2008, 5604; (*f*) J. J. Sánchez García, M. Flores-Alamo, M. A. Gallardo Vega and E. I. Klimova, *Mendeleev Commun.*, 2014, **24**, 274.
6 (*a*) B. A. Schweitzer and T. H. Koch, *J. Am. Chem. Soc.*, 1993, **115**, 5446; (*b*) S.-J. Zhang, J.-Q. Dong, and Y.-G. Wang, *Synth. Commun.*, 2003, **33**, 1891; (*c*) K. Piorecka, E. Radzikowska, J. Kurjata, K. Rozga-Wijas, W. A. Stanczyk and E. Wielgus, *New J. Chem.*, 2016, **40**, 5997; (*d*) K. H. Bouhadir, G. M. Kruger, K. Y. Lee and D. J. Mooney, *J. Pharm. Sci.*, 2000, **89**, 910.
7 (*a*) P. Zhao, J.-Z. Lu, J. He, W.-H. Chen, P.-P. Chen, D.-W. Chen and Q.-Y. Bin, *Nucleosides Nucleotides Nucleic Acids*, 2014, **33**, 597; (*b*) P. Zhao, S. Jin, J.-Z. Lu, J. Lv, G. Wu, P.-P. Chen, C.-L. Tan and D.-W. Chen, *Spectrochim. Acta, Part A*, 2015, **137**, 227.
8 L. N. Jungheim, T. A. Shepherd and J. K. Kling, *Heterocycles*, 1993, **35**, 339.
9 (*a*) M. Israel and G. Potti, *J. Med. Chem.*, 1982, **25**, 187; (*b*) G. Zhang, L. Fang, L. Zhu, D. Sun and P. G. Wang, *Bioorg. Med. Chem.*, 2006, **14**, 426; (*c*) X. Dang, Q. Liu, F. Cui, L. Qin, G. Zhang, X. Yao and J. Du, *Carbohydr. Res.*, 2011, **346**, 949; (*d*) F. Matsuda, T. Matsumoto, M. Ohsaki and S. Terashima, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 2983.
10 (*a*) A. Csorvási, K. E. Kövér, M. M. Menyhárt, F. Sztaricskai, Y. V. Dobrynin and T. G. Nikolaeva, *Arch. Pharm.*, 1998, **331**, 265; (*b*) J.-B. Ducep, D. Farge, G. Ponsinet and D. Reisdorf, *US Patent 4185111*, 1980.
11 (*a*) E. Bakina, Z. Wu, M. Rosenblum and D. Farquhar, *J. Med. Chem.*, 1997, **40**, 4013; (*b*) S. Ghirmai, E. Mume, V. Tolmachev and S. Sjöberg, *Carbohydr. Res.*, 2005, **340**, 15; (*c*) M. Masquelier, G. Tirzitis, C. O. Peterson, M. Palsson, A. Amolins, M. Plotniece, A. Plotniece, N. Makarova and S. G. Vitols, *Eur. J. Med. Chem.*, 2000, **35**, 429.
12 M. Sato, H. Kono and M. Shiga, I. Motoyama, K. Hata, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 252.
13 G. L. Tong, H. Y. Wu, T. H. Smith and D. W. Henry, *J. Med. Chem.*, 1979, **22**, 912.

Received: 28th February 2017; Com. 17/5188