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LETTERS TO THE EDITOR

Reactions of Benzofuroxans with Aminoalkyltriphenylphosphonium Bromides

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Furoxan and benzofuroxan derivatives functionalized with pharmacophore fragments (known as hybrid compounds) have attracted emerging interest [1].

Herein we report on studies involving super electrophilic benzofuroxans: 4,6-dichloro-5-nitrobenzofuroxan **IIa**, 7-chloro-4,6-dinitrobenzofuroxan **IIb**, and 5,7-dichloro-4,6-dinitrobenzylfuroxan **IIc**. Those compounds contained electron-withdrawing nitro groups increasing the reactivity of benzofuroxans towards nucleophiles and easily eliminating chlorine atoms allowing modification of the molecules with various pharmacophore moieties [2].

In order to study the possibility of targeted delivery of benzofuroxan molecules acting as biologically active fragments to mitochondria, we modified their molecules with 4-aminobutyltriphenylphosphonium bromide **Ia** and 4-aminodecyltriphenylphosphonium bromide **Ib** [3]. Butane and decane chains were chosen as linkers in amines, since the shorter chain length would result in deterioration of the ions permeability through the membrane [4].

Ability of phosphonium ions to selectively penetrate into mitochondria and deliver antioxidant was demonstrated for the first time in [5]. Triphenylphosphonium cation provided transport of the biologically active moiety through the mitochondrial membrane and efficient antioxidant protection.

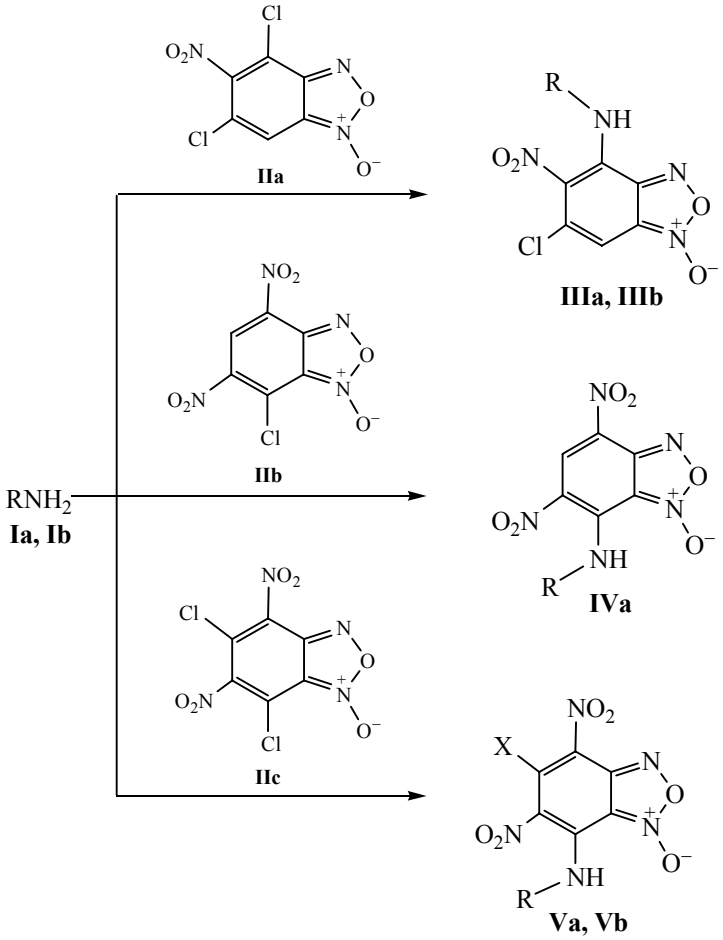
The reactions of super electrophilic benzofuroxans **IIa**–**IIc** with amines **Ia** and **Ib** yielded the hybrid benzofuroxan derivatives **III**–**V**. Noteworthily, in the case of benzofuroxan **IIb**, the monosubstituted **Vb** or disubstituted **Va** derivative could be formed (Scheme 1).

Structure and composition of the synthesized compounds were confirmed by IR and NMR spectroscopy, mass spectrometry (MALDI-TOF), and elemental analysis data.

[4-(6-Chloro-5-nitro-1-oxybenzo[1,2,5]oxadiazol-4-yl-amino)butyl]triphenylphosphonium bromide (IIIa). A solution of 0.0002 mol of the amine in 2 mL of DMSO was added to a solution of 0.05 g (0.0002 mol) of 4,6-dichloro-5-nitrobenzofuroxan **IIa** in 2 mL of DMSO upon stirring. The reaction mixture was stirred during 3 h and then poured into distilled water. The precipitate was filtered off, washed with hot water and diethyl ether, and dried in vacuum (0.06 mmHg) at 40°C to constant mass. Yield 45%, mp 100°C (hexane). IR (Vaseline oil), ν, cm^{-1}: 1552 (NO_2), 1625 (furoxan ring), 3270 (NH). ^1H NMR spectrum, ($CDCl_3$), δ, ppm, (*J*, Hz): 1.86 m (2H, $CH_2C\underline{H}_2P$), 2.11 m (2H, $C\underline{H}_2CH_2P$), 3.64 m (2H, $C\underline{H}_2CH_2N$), 4.13 t (2H, $CH_2C\underline{H}_2N$, $^3J_{HH}$ 7.06), 6.54 s (1H, Ar), 7.69 m (15H, Ar), 8.25 s (1H, NH). ^{31}P NMR spectrum, ($CDCl_3$): δ_P 24.14 ppm. Mass spectrum (MALDI), *m*/*z*: 648 $[M + K]^+$. Found, %: C 53.39; H 4.25; Br 12.90; Cl 5.34; N 9.07; P 4.75. $C_{28}H_{25}BrClN_4O_4P$. Calculated, %: C 53.56; H 4.01; Br 12.73; Cl 5.65; N 8.92; P 4.93

[10-(6-Chloro-5-nitro-1-oxybenzo[1,2,5]oxadiazol-4-yl-amino)decyl]triphenylphosphonium bromide

Scheme 1.



X= RNH (**Va**), Cl (**Vb**); R = $C_4H_8P^+(Ph)_3Br^-$ (**a**), $C_{10}H_{20}P^+(Ph)_3Br^-$ (**b**).

(IIIb) was prepared similarly. Yield 43%, orange oil. IR (KBr), ν, cm^{-1}: 1553 (NO_2), 1623 (furoxan ring), 2854 (CH_2), 3088 (CH_{Ar}), 3331 (NH). ^1H NMR spectrum, (DMSO-d_6), δ, ppm: 0.88 m (2H, CH_2P), 1.27 m (14H, CH_2), 1.79 m (2H, $C\underline{H}_2CH_2N$), 3.58 m (2H, $CH_2C\underline{H}_2N$), 7.80 m (6H, Ar), 7.93 m (9H, Ar), 8.15 s (1H, Ar), 8.25 s (2H, NH). ^{31}P NMR spectrum, (DMSO-d_6): δ_P 23.96 ppm. Mass spectrum (MALDI), *m*/*z*: 631 $[M - Br]^+$. Found, %: C 57.70; H 5.00; Cl 4.81; Br 11.50; N 7.60; P 4.63. $C_{34}H_{37}BrClN_4O_4P$. Calculated, %: C 57.35; H 5.24; Cl 4.98; Br 11.22; N 7.87; P 4.35.

[4-(5,7-Dinitro-3-oxybenzo[1,2,5]oxadiazol-4-ylamino)butyl]triphenylphosphonium bromide (IVa). A solution of 0.0006 mol of the amine in 2 mL of methanol was added to a solution of 0.15 g (0.0006 mol) of 7-chloro-4,6-dinitrobenzofuroxan **IIb** in 2 mL of methanol upon stirring. The reaction mixture was stirred during 1 h at 60°C. The precipitate was separated, washed sequentially with hot water and diethyl ether, and dried in vacuum (0.06 mmHg) at 40°C to constant mass. Yield 50%, mp 30°C. IR (KBr), ν, cm^{-1}: 1654 (furoxan ring), 3064 (CH_{Ar}), 3236 (NH). ^1H NMR spectrum, (DMSO-d_6), δ, ppm, (*J*, Hz): 2.03 t (2H, CH_2P, $^3J_{HH}$ 9.46), 3.58 m (4H, C_2H_4), 4.20 t (2H, CH_2N, $^3J_{HH}$ 9.12), 7.72 m (15H, Ar), 8.73 s (1H, Ar), 10.77 t (1H, NH, $^3J_{HH}$ 8.92). ^{31}P NMR spectrum, (DMSO-d_6): δ_P 25.25 ppm. Mass spectrum (MALDI), *m*/*z*: 558 $[M - Br]^+$. Found, %: C 52.90; H 3.63; Br 12.80; N 10.79; P 4.95. $C_{28}H_{25}BrN_5O_6P$. Calculated, %: C 52.68; H 3.95; Br 12.52; N 10.97; P 4.85.

4,6-Bis[(4-aminobutyl)triphenylphosphonium bromide]-5,7-dinitro-3-oxybenzo[1,2,5]oxadiazol-1-oxide (Va) was prepared similarly. Yield 46%, mp 30°C. IR (Vaseline oil), ν, cm^{-1}: 1377 (NO_2, sym.), 1550 (NO_2, asym.), 1639 (furoxan ring). ^1H NMR spectrum,

(acetone-d_6), δ, ppm, (J, Hz): 3.21 q (2H, CH_2P, $^3J_{HH}$ 8.65), 3.37 m (6H, C_3H_6), 7.76–7.89 m (30H, Ar). ^{31}P NMR spectrum, (DMSO-d_6): δ_P 23.89 ppm. Mass spectrum (MALDI), m/z: 913 $[M + Na - HBr]^+$. Found, %: C 57.10; H 4.75; Br 14.78; N 7.60; P 5.68. $C_{50}H_{52}Br_2N_6O_6P_2$. Calculated, %: C 56.94; H 4.97; Br 15.15; N 7.97; P 5.87.

[10-(5-Chloro-4,6-dinitro-1-oxybenzo[1,2,5]oxadiazol-4-yl-amino)decyl]triphenylphosphonium bromide (Vb) was prepared similarly. Yield 59%. IR (KBr), ν, cm^{-1}: 1357 (NO_2, sym.), 1546 (NO_2, asym.), 1638 (furoxan ring), 2854 (CH_2), 3060 (CH_{Ar}), 3385 (NH). ^1H NMR spectrum, ($CDCl_3$), δ, ppm, (J, Hz): 1.23–1.64 m (18H, C_9H_{18}), 3.25 s (2H, CH_2N), 7.67 d (15H, Ar, $^3J_{HH}$ 7.62). ^{31}P NMR spectrum, (DMSO-d_6): δ_P 23.8 ppm. Mass spectrum (MALDI), m/z: 745 $[M + Na]^+$. Found, %: C 60.70; H 6.54; Br 13.38; N 7.30; P 6.00. $C_{62}H_{76}Br_2N_6O_6P_2$. Calculated, %: C 60.89; H 6.26; Br 13.07; N 7.47; P 5.76.

^1H NMR spectra were recorded using a Bruker MSL-400 spectrometer (400.13 MHz) relative to residual proton signals of the deuterated solvents. ^{31}P NMR spectra were registered with a Bruker MSL-400 spectrometer (161.94 MHz) relative to external 85% H_3PO_4. Mass spectra (MALDI) were recorded with an UltraFlex III TOF/TOF (Bruker Daltonik GmbH). Melting points were determined using a Boetius apparatus. TLC analysis was performed on Silufol UV 254 plates (Kavalier). Elemental analysis was carried out using a Carlo-Erba EA 1108 analyzer.

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