Supporting Information

A novel amphiphilic fluorescent probe BODIPY—O-CMC—cRGD as nanoparticle vector

Tingting Zhu, Ji Xiong, Zhongbo Xue, Yu Su, Fengnan Sun, Ran Chai, Jialiang Xu, Yaqing Feng, Shuxian Meng

Experiment:

Synthesis

Compound 1: ethyl 6-(4-formylphenoxy) hexanoate

A mixture of 4-hybroxybenzaldehyde derivative (2.440 g, 20 mmol) and ethyl 6-bromohexanoate (4.906 g, 22 mmol) was refluxed in dry aceton for 12 h in the presence of potassium carbonate. The crude mixture was filtered to remove remaining K₂CO₃. The resulting solution was concentrated in vacuo and purified by silica gel column chromatography by using CH₂Cl₂/hexane. ¹H NMR (400 MHz, CDCl₃, δ in ppm): δ=9.87(s,1H), 7.82(d, J=8.8 Hz, 2H), 6.98(d, J=8.6 Hz, 2H), 4.13(q, J=7.1 Hz, 2H), 4.05(t, J=6.4 Hz, 2H), 2.32(t, J=7.5 Hz, 2H), 1.84(m, 2H), 1.72(m, 2H), 1.52(m, 2H), 1.27(t, J=7.0 Hz, 3H). MALDI-TOF MS calcd for C₂₃H₂₅O₄ 264.32, found 264.7892.

Compound 2: ethyl 6-(4-(3,7-dibromo-5,5-difluoro-3,7-bis(4-methoxyphenyl)-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)phenoxy)hexanoate

This compound was prepared in a sequence of steps in one pot reaction. Compound 1 (2.640 g, 10 mmol) and 2.5 equivalent of pyrrole (1.68 g, 25 mmol) was dissolved in dry CH₂Cl₂ under nitrogen in an ice bath over 1 h and stirred for another 1 h. When the reaction mixture was warmed to room temperature, 5 min, then 6 mL of BF₃·Et₂O was added dropwise. The mixed solution was refluxed for 1 h. The reaction mixture was washed with 0.1 M NaOH solution and methylene dichloride successively. The organic layers were dried over MgSO₄ and concentrated in vacuo. The crude compound was filtered by flash column. The residue was purified by chromatography on a silica gel by using dichloromethane/hexane.

δ=7.73(d, J=8.8 Hz, 2H), 7.68(d, J=8.8 Hz, 2H), 7.28(d, J=4.4 Hz, 2H), 6.72(d, J=4.4 Hz, 4.09(d, J=2.6 Hz, 2H), 4.03(d, J=2.8 Hz, 2H), 2.00(d, J=7.7 Hz, 2H), 1.34(d, J=7.4 Hz, 2H) 1.06(t, J=7.0 Hz, 3H), 1.41(d, J=7.2 Hz, 2H). MALDI-TOF MS calcd for C₃₅H₃₉BBrF₅N₂O₁₅ 582.01, found 583.2376.

Compound 3: ethyl 6-(4-(5,5-difluoro-3,7-bis(4-methoxyphenyl)-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)phenoxy)hexanoate

Compound 2, 4-methoxyphenylboronic acid (2.9 g, 5 mmol), and K₂CO₃ (1.38 g, 10 mmol) was dissolved in the solvent pair(toluene/water) in a 100 ml round-bottomed flask fitted with a reflux condenser. After bubbling with nitrogen for half an hour, a catalytic amount of Pd(PPh₃)₄ (3.5 mg) was added and the reaction mixture was refluxed at 85 °C for 8 h. The system was cooled to room temperature and then extracted with CH₂Cl₂/H₂O twice. The organic layer was then dried with MgSO₄ and evaporated in vacuum. The residue was subjected to chromatography on a silica gel by using dichloromethane/hexane. ¹H NMR (400 MHz, CDCl₃, δ in ppm): δ=7.90(d, J=8.7 Hz, 4H), 7.46(d, J=2.4 Hz, 2H), 6.88(d, J=8.7 Hz, 4H), 6.78(d, J=4.0 Hz, 2H), 6.62(d, J=4.4 Hz, 2H), 6.53(d, J=4.3 Hz, 2H), 4.10(t, J=7.5 Hz, 2H), 7.51(d, J=4.1 Hz, 2H), 7.04(d, J=7.1 Hz, 1H), 6.83(d, J=2.1 Hz, 1H), 6.61(d, J=4.4 Hz, 2H), 6.95(d, J=8.9 Hz, 4H), 4.07(t, J=6.2 Hz, 2H), 3.85(s, 6H), 1.62(m, 2H), 1.53(m, 2H), 1.30(m, 2H). MALDI-TOF MS calcd for C₃₅H₃₉BrF₆N₂O₁₆ 638.28, found 638.2170.

Compound 4: ethyl 6-(4-(5,5-difluoro-3,7-bis(4-methoxyphenyl)-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)phenoxy)hexanoate

The compound 3 (1.276 g, 2 mmol) and KOH (4.704 g, 84 mmol) were added dropwise over 10 min. The reaction was monitored by TLC. The organic solvent was removed on a rotary evaporator under vacuum. The intermediate product was purified by flash column chromatography using CH₂Cl₂ to collect the red intermediate product. A solution of collected intermediate product and triethylamine (2 ml) in dry toluene was stirred about 5 min, then 6 mL of BF₃·Et₂O was added dropwise. The mixed solution was refluxed for an 1 h. The reaction mixture was washed with 0.1 M NaOH solution and methylene dichloride successively. The organic layers were dried over MgSO₄ and concentrated in vacuo. The crude compound was purified by flash column. The residue was purified by silica gel column chromatography by using dichloromethane/petroleum ether and the needed red powder compound. ¹H NMR (400 MHz, DMSO-d₆, δ in ppm) δ=7.73(d, J=8.8 Hz, 2H), 7.68(d, J=8.8 Hz, 2H), 7.28(d, J=4.4 Hz, 2H), 6.72(d, J=4.4 Hz, 2H), 4.09(d, J=2.6 Hz, 2H), 4.03(d, J=2.8 Hz, 2H), 2.00(d, J=7.7 Hz, 2H), 1.34(d, J=7.4 Hz, 2H) 1.06(t, J=7.0 Hz, 3H), 1.41(d, J=7.2 Hz, 2H). MALDI-TOF MS calcd for C₃₅H₃₉BBrF₅N₂O₁₅ 582.01, found 583.2376.

BODIPY dye: 2,5-dioxopyrroloidin-1-yl 6-(4-(5,5-difluoro-3,7-bis(4-methoxyphenyl)-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)phenoxy)hexanoate
The compound 4 (0.61 g, 1 mmol), N-hydroxysuccinimide (0.23 g, 2 mmol), dimethylaminopyridine (DMAP) (0.244 g, 2 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.382 g, 2 mmol) were dissolved in dry dichloromethane at 35°C for 2 h. After that, the mixture was washed with 2 × 10 mL of water, the organic phase was dried with MgSO₄ and evaporated in vacuum. The crude product was purified by chromatography on silica gel by using dichloromethane/hexane.

$^1$H NMR (400MHz, CDCl₃, δ in ppm): 7.87(d, J=5.2 Hz, 4H), 7.07(d, J=2.4 Hz, 2H), 7.52(d, J=2.4 Hz, 2H), 6.97(d, J=8 Hz, 4H; Ar), 6.6(d, J=4.4 Hz, 2H), 4.10(t, J=3.85 Hz), 6.88(d, J=4.6, 2H), 3.80(s, 6H), 4.10(t, J=9.2 Hz), 3.98(t, J=2.5 Hz), 2.68(s, 2H), 2.58(s, 2H), 2.33(s, 2H), 1.78-1.55 (m, 6H). MALDI-TOF MS calcd for C₃₉H₃₆BF₂N₃O₇: 707.54, found 707.8739.