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SUPPORTING INFORMATION

Pre-targeting with ultra-small nanoparticles: Boron carbon dots as drug candidates for boron neutron capture therapy.

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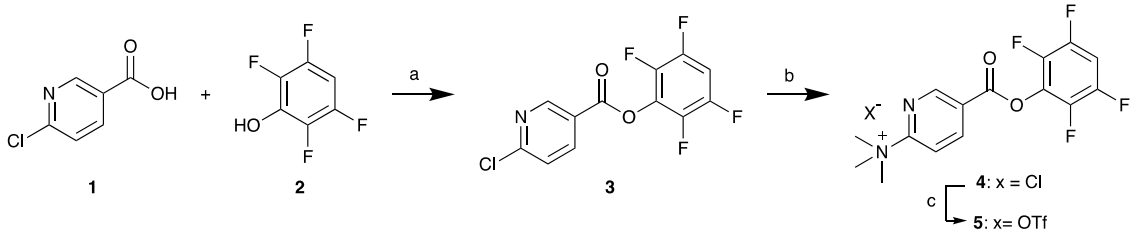
Synthesis of [^{18}F]FPyTFP precursor 4

The precursor for the preparation of [^{18}F]FPyTFP was synthesized in a 3-step sequence as described previously (see Scheme S1).[1]



Scheme S1. Schematic representation of the synthetic route for the preparation of [^{18}F]FPyTFP precursor 4.

In brief, a solution of 6-chloronicotinic acid (**1**, 900 mg, 5.7 mmol), 2,3,5,6-tetrafluorophenol (**2**, 750 mg, 4.5 mmol) and *N,N'*-dicyclohexylcarbodiimide (1.9 g, 9 mmol) in dioxane (40 mL) was stirred at room temperature for 2 h. The mixture was filtered, the solvent evaporated, and the crude product crystallized from hot hexane (25 mL), to give 6-chloronicotinic acid 2,3,5,6-tetrafluorophenyl ester (**3**, 945 mg, 3.1 mmol; 69 %) as a white solid.

^{1}H NMR (500 MHz, Chloroform-d) δ 9.21 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.42 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.57 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.11 (tt, *J* = 9.8, 7.0 Hz, 1H) (matches the literature data).

6-chloronicotinic acid 2,3,5,6-tetrafluorophenyl ester (**3**, 760 mg, 2.5 mmol) was dissolved in trimethylamine solution in tetrahydrofurane (1 M, 20 mL) and stirred at room temperature for 5 h. The white precipitate was collected by vacuum filtration and washed with diethyl ether (2 × 5 mL) to obtain *N,N,N*-trimethyl-5-((2,3,5,6-tetrafluorophenoxy)carbonyl)pyridin-2-aminium chloride (**4**, 605 mg, 1.7 mmol; 68 %) as an off-white solid. This was suspended in trimethylsilyl triflate solution in dichloromethane (2 % w/w, 25 mL). The mixture was exposed to ultrasound for 10 min, the solvent was evaporated and the crude washed with diethyl ether (2 × 10 mL) to give *N,N,N*-trimethyl-5-((2,3,5,6-tetrafluorophenoxy)carbonyl)pyridin-2-aminium trifluoromethanesulfonate (**5**, 792 mg, 1.7 mmol; 100 %) as an off-white solid.

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 9.28 (d, *J* = 2.3 Hz, 1H), 8.79 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.37 (tt, *J* = 10.5, 7.3 Hz, 1H), 3.54 (s, 9H) (matches the literature data).

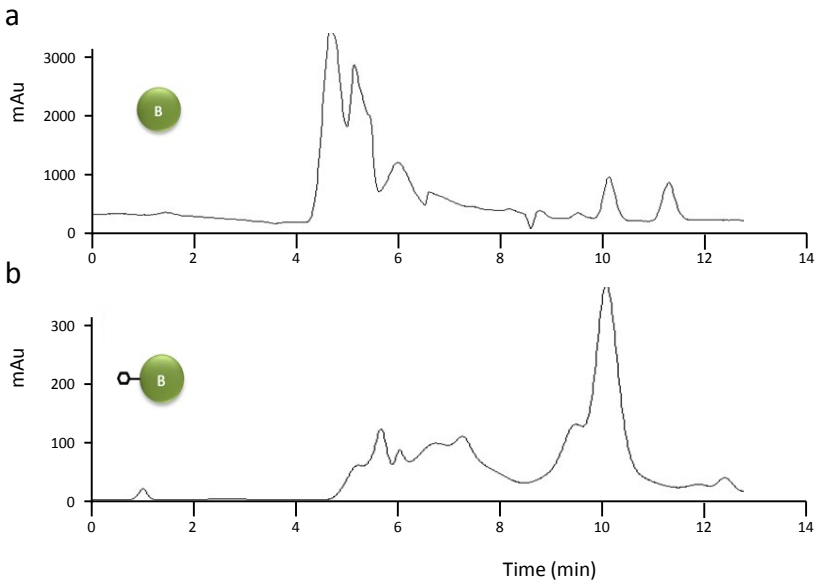


Figure S1: HPLC chromatograms representing naked B-CDs (a) and B-CDs-tz (b). HPLC analyses were carried out using an Agilent 1200 series HPLC equipped with a quaternary pump and a multiple wavelength detector (λ = 280 nm). A size exclusion column (TSKgel SuperOligo PW, 150 × 6 mm, 3 µm) was used as stationary phase and 0.1 M ammonium formate (pH = 6) as the mobile phase at a flow of 0.4 mL/min.

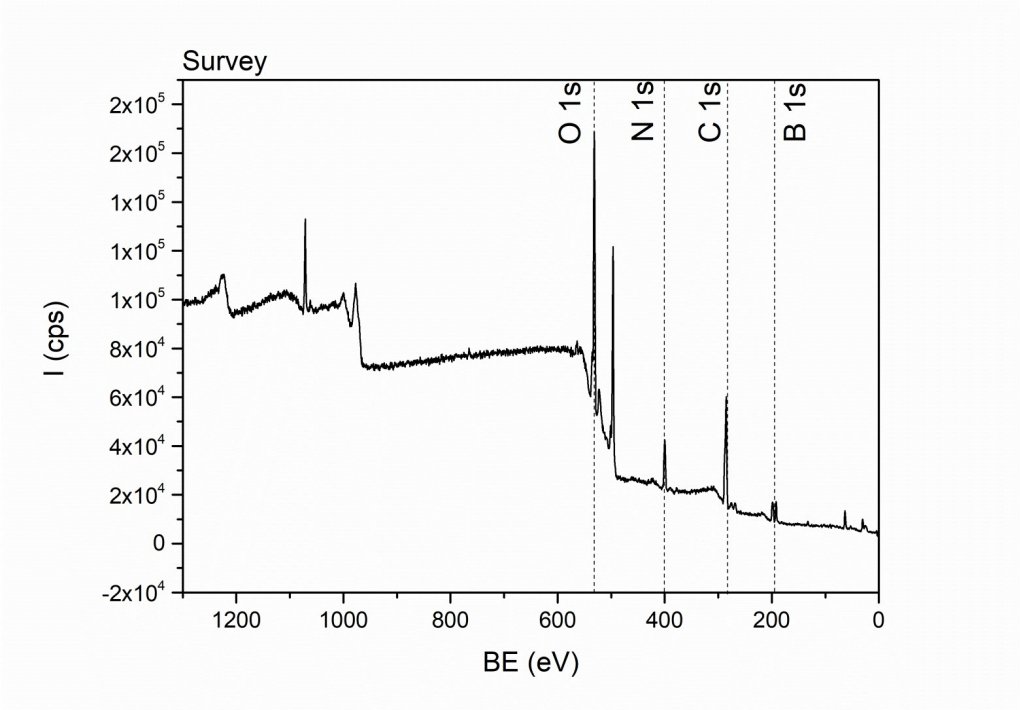


Figure S2: XPS survey spectrum of B-CDs, confirming the presence of boron.

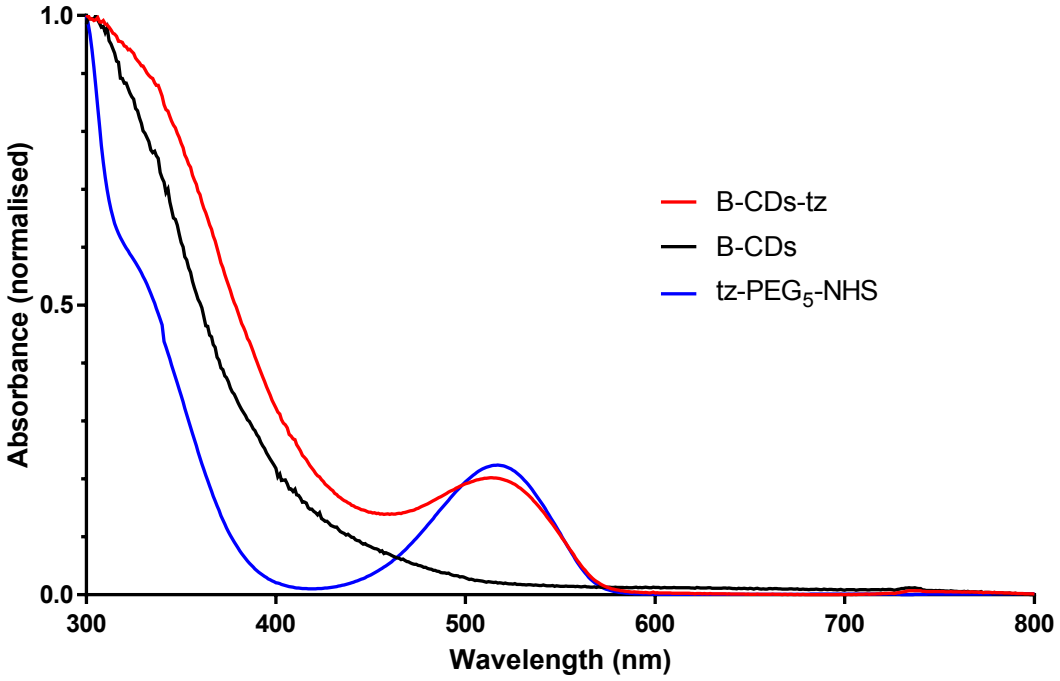


Figure S3: UV-Vis spectra for B-CDs-tz (red line), B-CDs (black line) and the free tz-PEG_5-NHS (blue line).

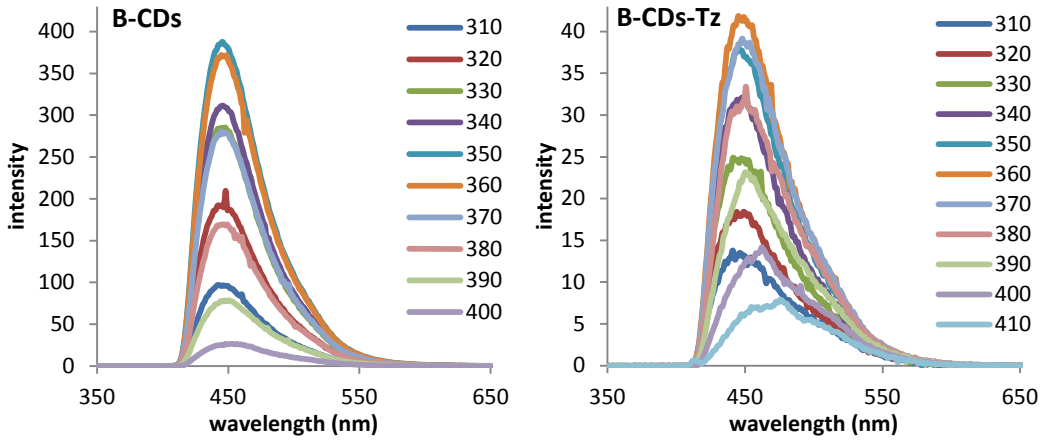


Figure S4: Emission spectra at different excitation wavelengths (310–410 nm) of B-CDs (left) and B-CDs-tz (right).

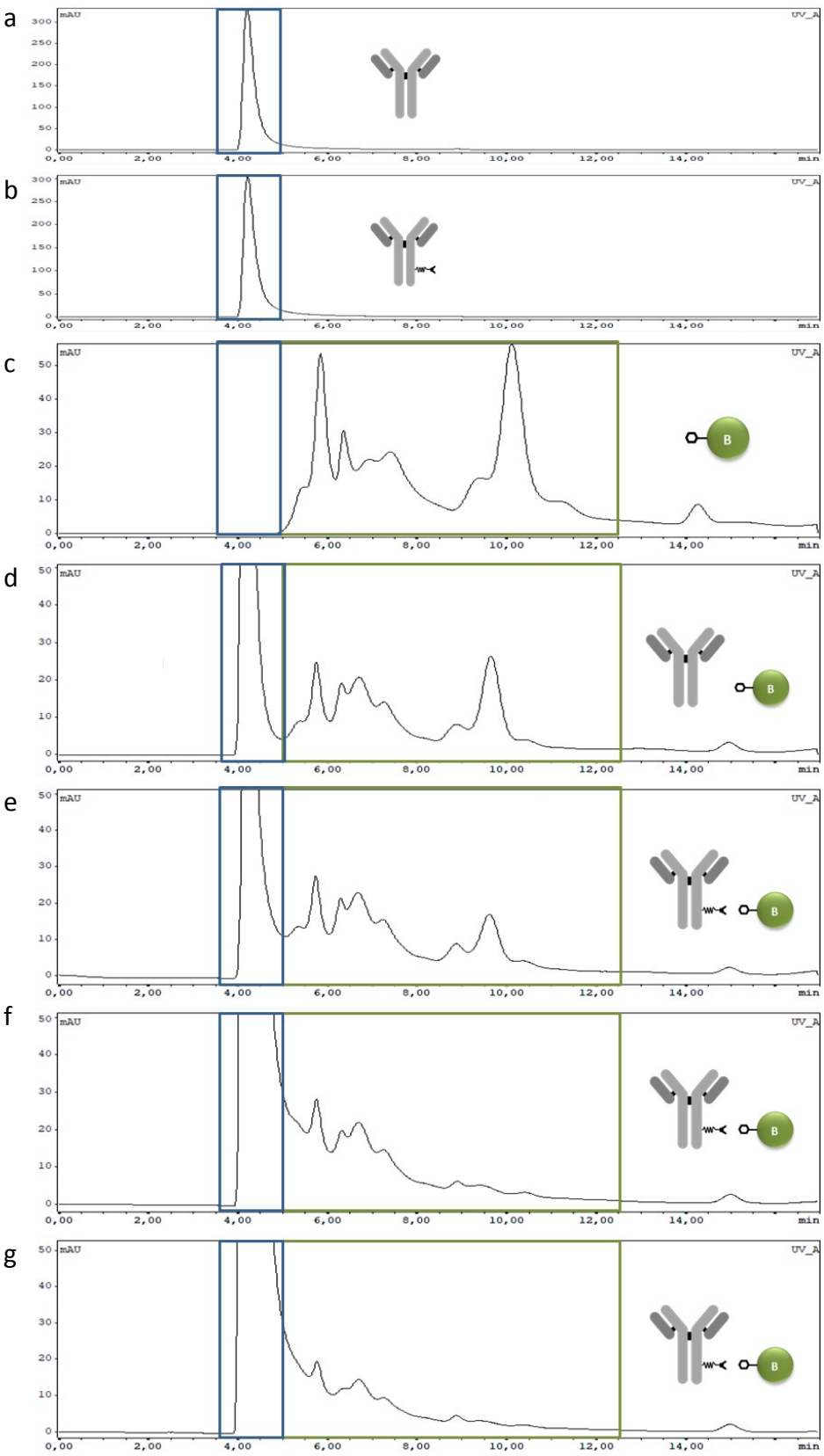


Figure S5: HPLC chromatograms to demonstrate occurance of click reaction between Trastuzumab-TCO and B-CDs-tz including control chromatograms. (a) Trastuzumab, (b) Trastuzumab-TCO, (c) B-CDs-tz, (d) control of non-functionalized Trastuzumab and B-CDs-tz in a ratio of 2:1, (e-g) Trastuzumab-TCO and B-CDs-tz in a ratio of (e) 2:1, (f) 20:1, (g) 50:1. HPLC conditions are the same as in Fig. S1.

REFERENCES

1. D. E. Olberg, J. M. Arukwe, D. Grace, O. K. Hjelstuen, M. Solbakken, G. M. Kindberg and A. Cuthbertson, *J. Med. Chem.*, 2010, **53**, 1732-1740.