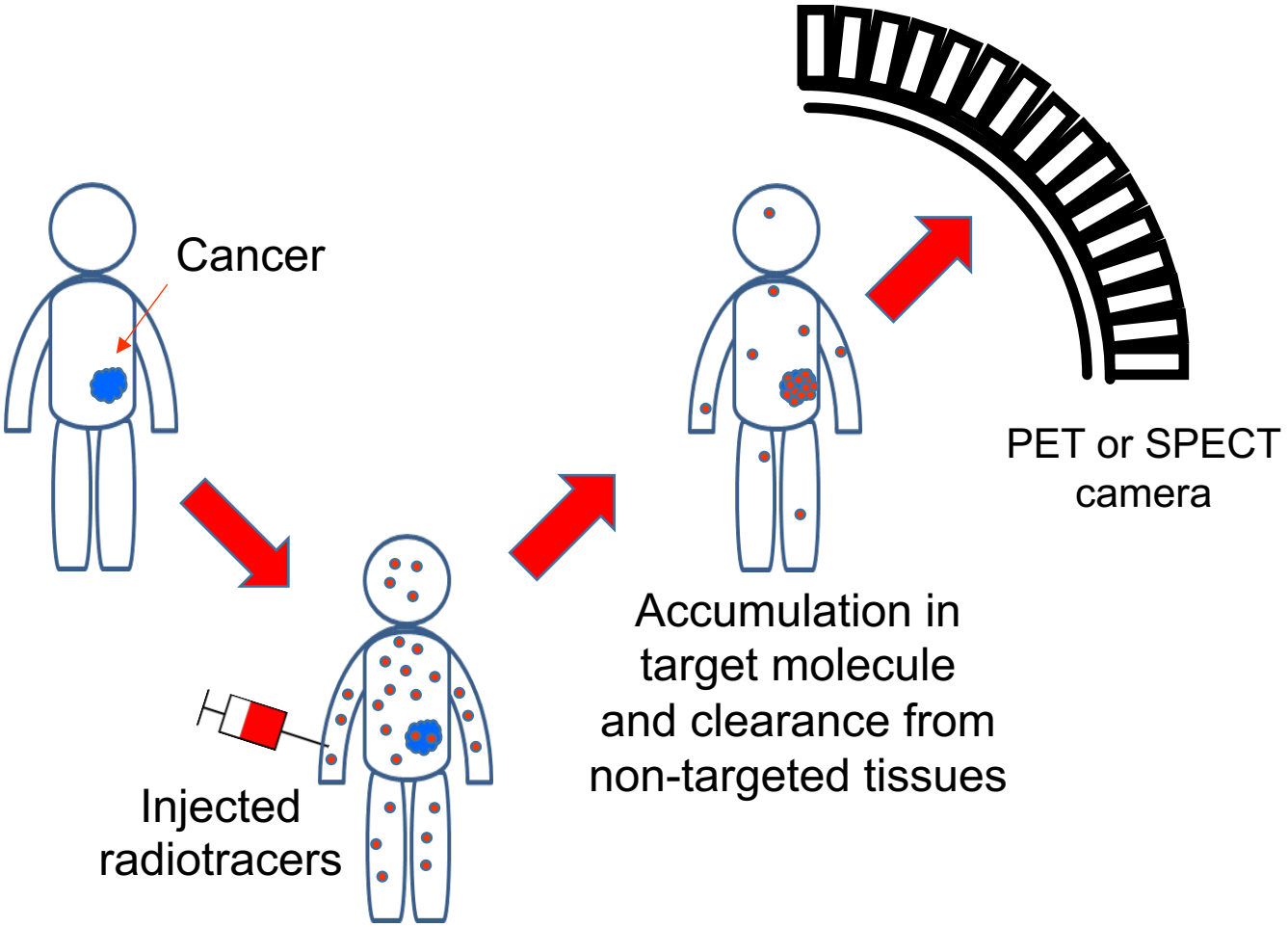
Synthesis and evaluation of new radiotracers for PDGFRβ imaging

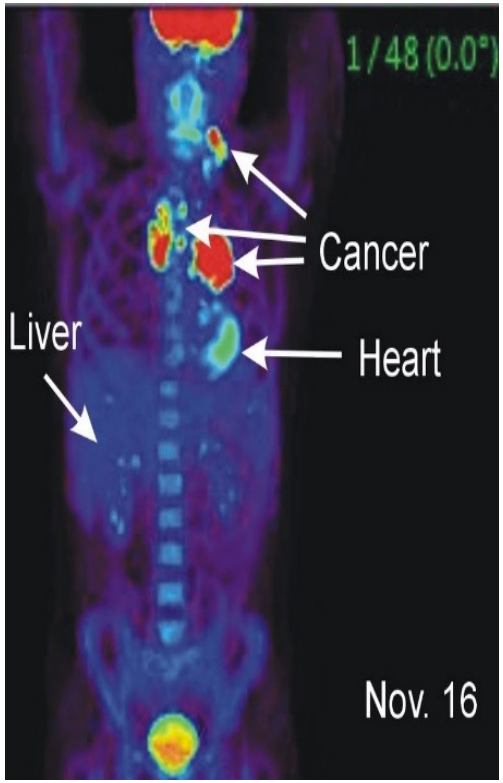
◯Nurmaya Effendi[1], Kazuma Ogawa[1, 2], Kenji Mishiro[2], Takeshi Takarada[3], Daisuke Yamada[3], Yoji Kitamura[4], Kazuhiro Shiba[4], Akira Odani[1]

[1]Pharmaceutical Sciences, Kanazawa University,
[2]Institute for Frontier Science Initiative, Kanazawa University,
[3]Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University,
[4]Advanced Science Research Centre, Kanazawa University

Concept of diagnostic radiopharmaceuticals

Positron-emitting radionuclides: ^{18}F, ^{13}N, ^{11}C, ^{15}O, ^{76}Br, ^{68}Ga
Single photon-emitting radionuclides: ^{123}I, ^{99m}Tc, ^{67}Ga, ^{111}In





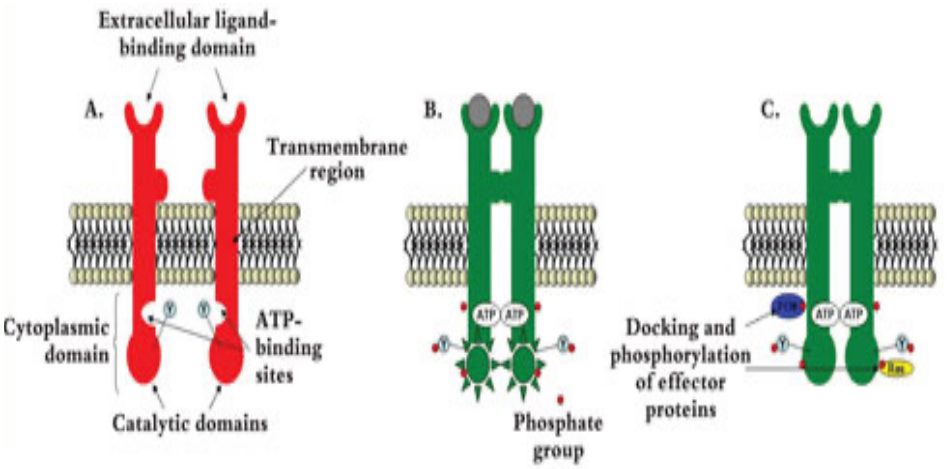
PET (Positron emission tomography)
SPECT (Single photon emission computed tomography)

http://mediumtimes.blogspot.jp/2011/01/

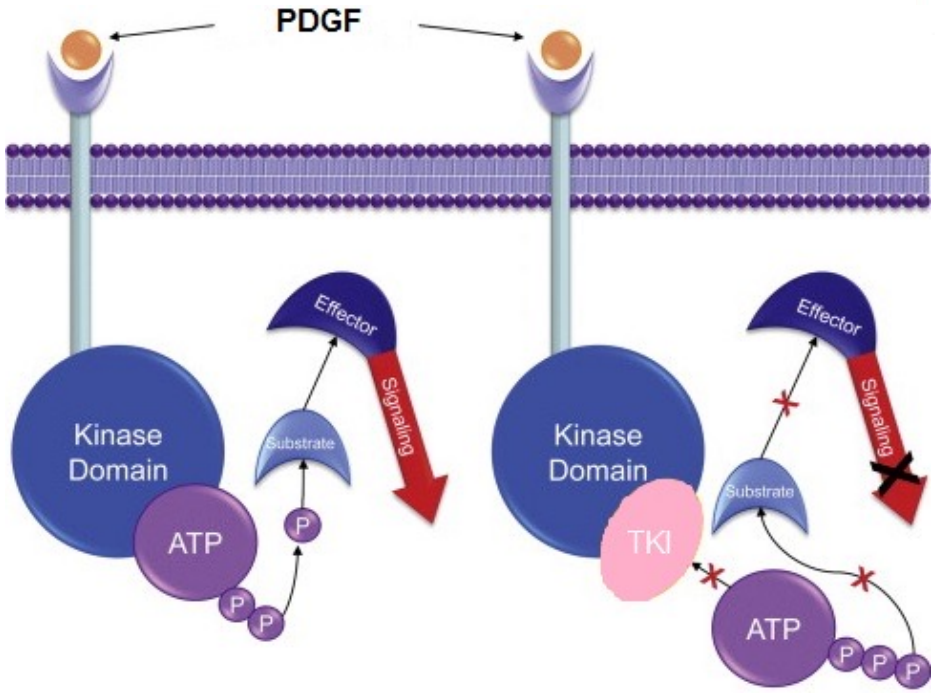
General introduction

PDGFRβ is one of receptor tyrosine kinases.

PDGFRβ could be an attractive target not only for cancer therapy but also developing tumor-imaging agents.



* US Pharm. **2008**; 33(10)(Oncology suppl):3-14



Cancer Treat Rev. ***2011****, 37, 373-384*

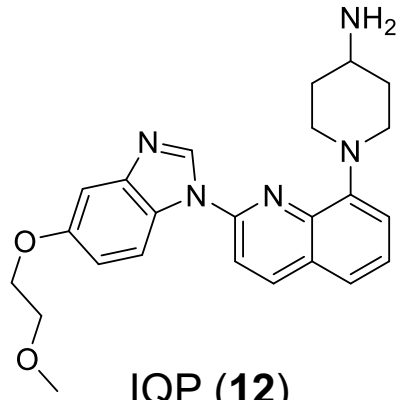
Radiolabeled TKI targeted ATP binding site might be meaningful to:

1. evaluate the drug sensitivity,
2. assess the mutation status of receptor target,
3. be a useful tool in drug development.

General introduction

CP-673,451 (IQP) is a benzimidazole-quinoline derivative and a potent inhibitor of PDGFR kinase with IC_{50} = 1.0 nM for PDGFRβ, 10.0 nM for PDGFRα, and >1000 times selective versus a variety of other kinases.[1,2]

IQP competitively inhibits binding of ATP into ATP binding site of PDGFRβ and blocks phosphorylation.[1]



IQP (**12**)

We speculated that radioiodinated IQP derivatives might be useful as PDGFRβ imaging agents.

[1]*Cancer Res.* ***2005***, *65, 957-966*
[2]*Onco Targets Ther.* ***2014***, *7, 1215-1221*

Introduction

1. Isotopes of the same element have the same chemical properties and act in the same way in chemical and biological reactions.

2. Various radioisotopes of iodine[1]

Isotope	Decay mode (%)	Half-life	Application
^{123}I	EC (100)	13.2 h	SPECT imaging
^{124}I	β+ (22), EC (78)	4.8 d	PET imaging
^{125}I	EC (100)	59.4 d	Auger electron therapy, basic research
^{131}I	β$^-$ (90), EC (10)	8.0 d	Radiotherapy

β+ (positron emission), EC (electron capture), β$^-$ (electron emission)

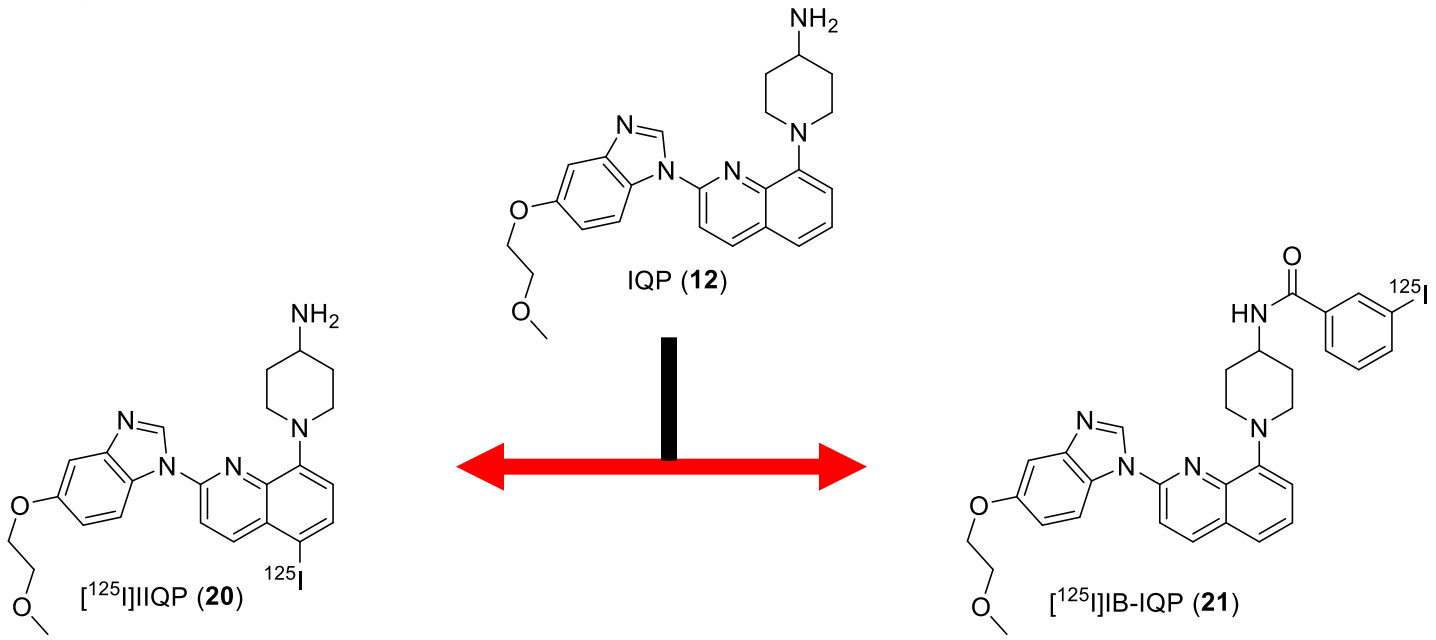
3. In this initial study, ^{125}I was used because of its relatively long half-life.

[1] *J Radioanal Nucl Chem.* ***2016***, *309, 859-889*

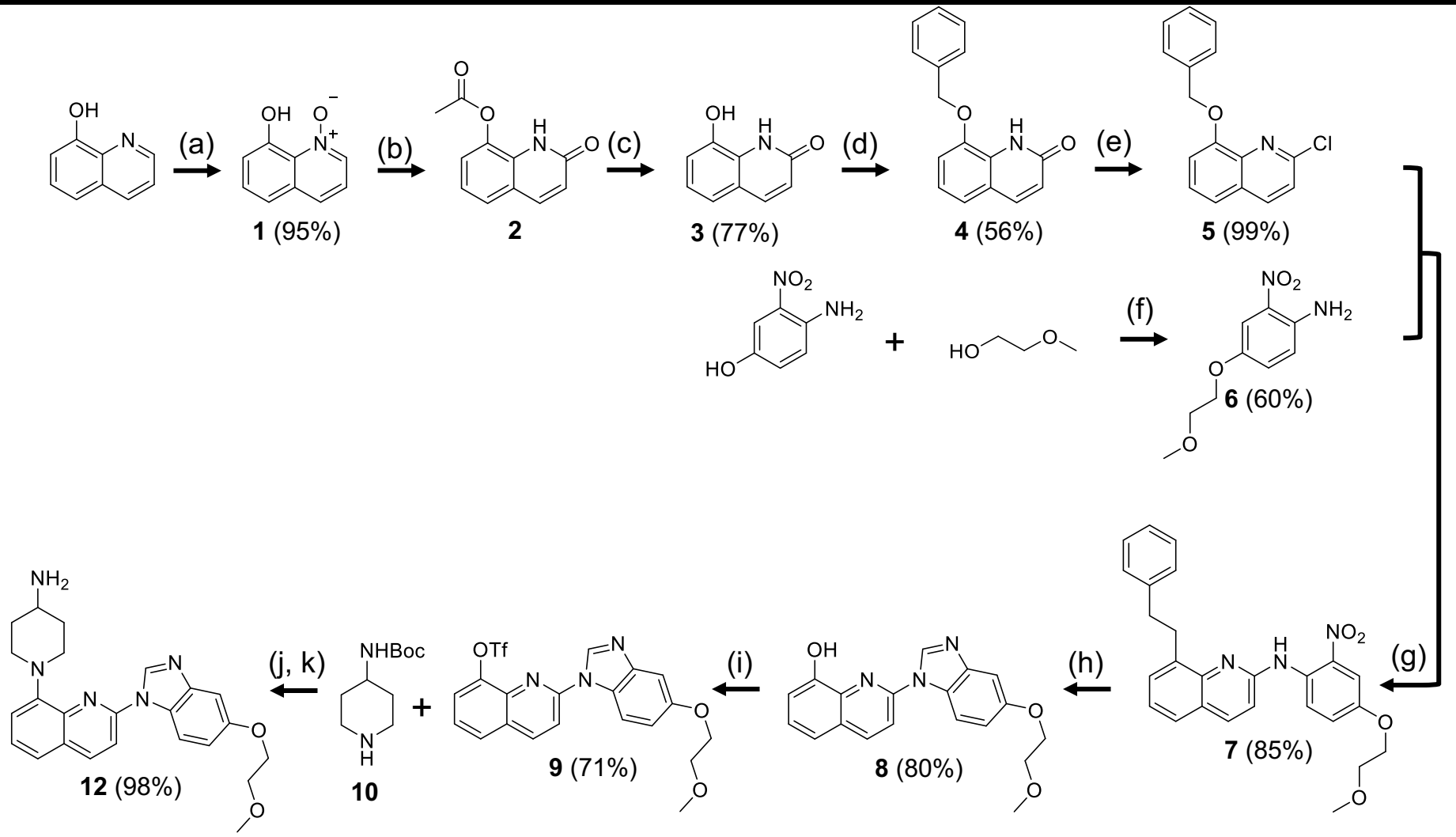
Strategy

1. Iodine was easily introduced into C-5 of quinoline group of IQP as a reactive site for halogenation to afford IIQP.

2. Iodine was indirectly incorporated into IQP wherein primary amine of piperidine group was linked with 3-iodo-benzoyl group to yield IB-IQP.



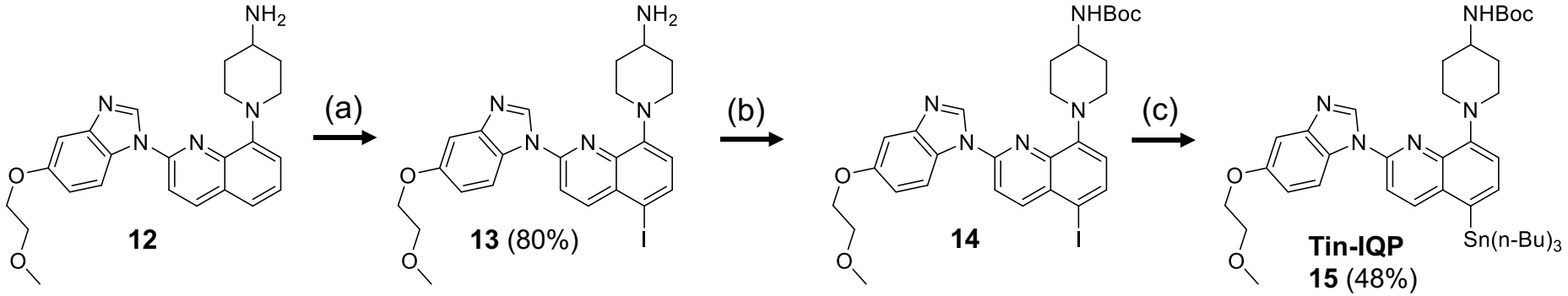
Synthesis of lead compound IQP



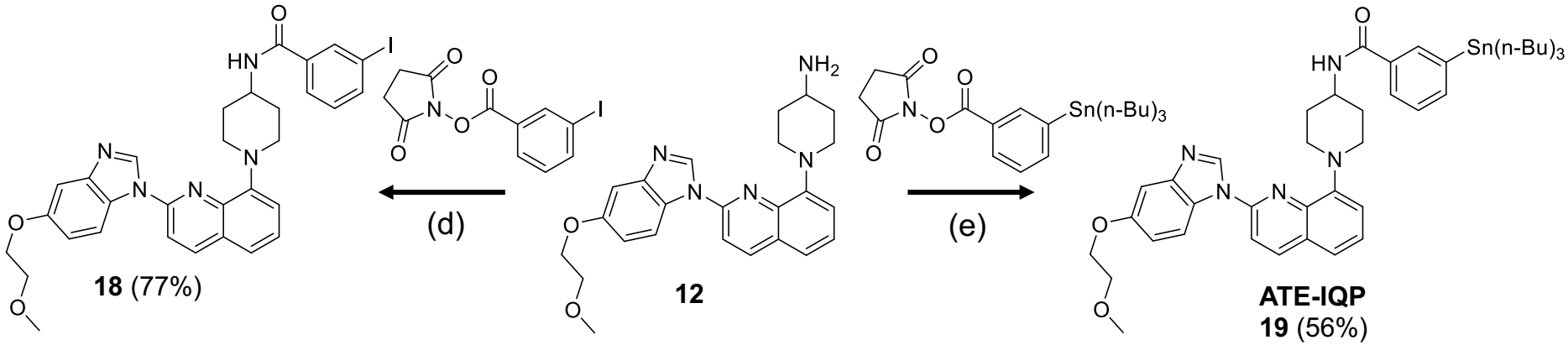
(a) sodium tungstate dihydrate, hydrogen peroxide, 75 °C, 5 h (b) acetic anhydrate, 100 °C, 7.5 h (c) HCl, 95 °C, 2 h (d) benzyl bromide, potassium carbonate, reflux, 6 h (e) $POCl_3$, reflux, 16 h (f) MsCl, cesium carbonate, reflux, 3 d (g) palladium acetate, DIPHOS, cesium carbonate, phenyl boronic acid, 115 °C, 3 d (h) palladium chloride, TEA, formic acid, formamidine acetate, reflux, overnight (i) *N*-phenyl-bis(trifluoromethanesulfonimide), room temperature, 2 d (j) cesium carbonate, rac-BINAP, tris(dibenzylideneacetone)dipalladium(0), reflux, 3 d (k) TFA, room temperature, 15 min.

Synthesis of reference compounds and precursors

1. Synthesis of IIQP (**13**) and tin-IQP (**15**)



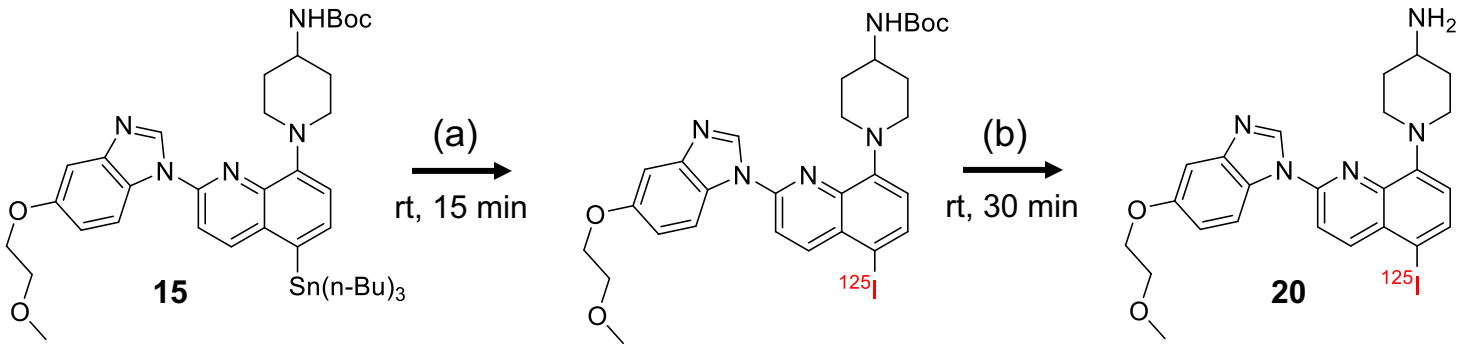
2. Synthesis of IB-IQP (**18**) and ATE-IQP (**19**)



(a) *N*-chlorosuccinimide (NCS), NaI, 50 °C, 18 h (b) Boc_2O, TEA, rt, 3 d (c) hexabutyldistannane, $Pd[P(C_6H_5)_3]_4$, reflux, 24 h, (d) 50 °C, 2 h; (e) 50 °C, 3 h

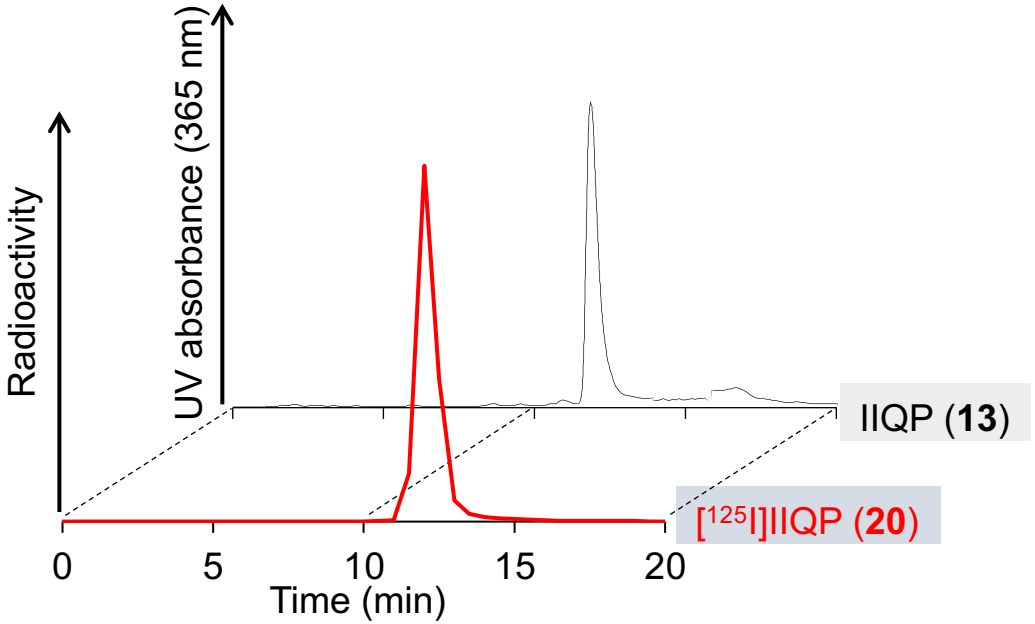
Preparation of [^{125}I]IIQP

Radiolabeling



(a) [^{125}I]NaI, NCS, acetic acid
(b) TFA

Chromatogram of [^{125}I]IIQP and IIQP



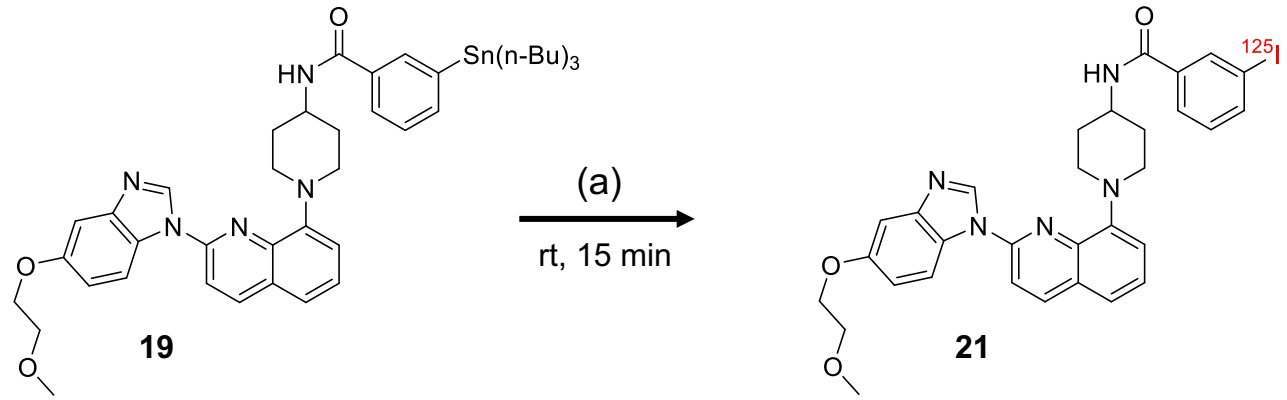
Radiochemical yield: 95.0%

Radiochemical purity: 99.5%

HPLC condition:
Column: 5C$_{18}$-MS-II (4.6 ID x 150 mm)
Mobile phase: (B) 70 – 90%, 0 – 20 min
A) 0.05% TEA in water
B) 0.05% TEA in MeOH
Flow rate: 1.0 mL / min
Temperature: 40 °C

Preparation of [^{125}I]IB-IQP

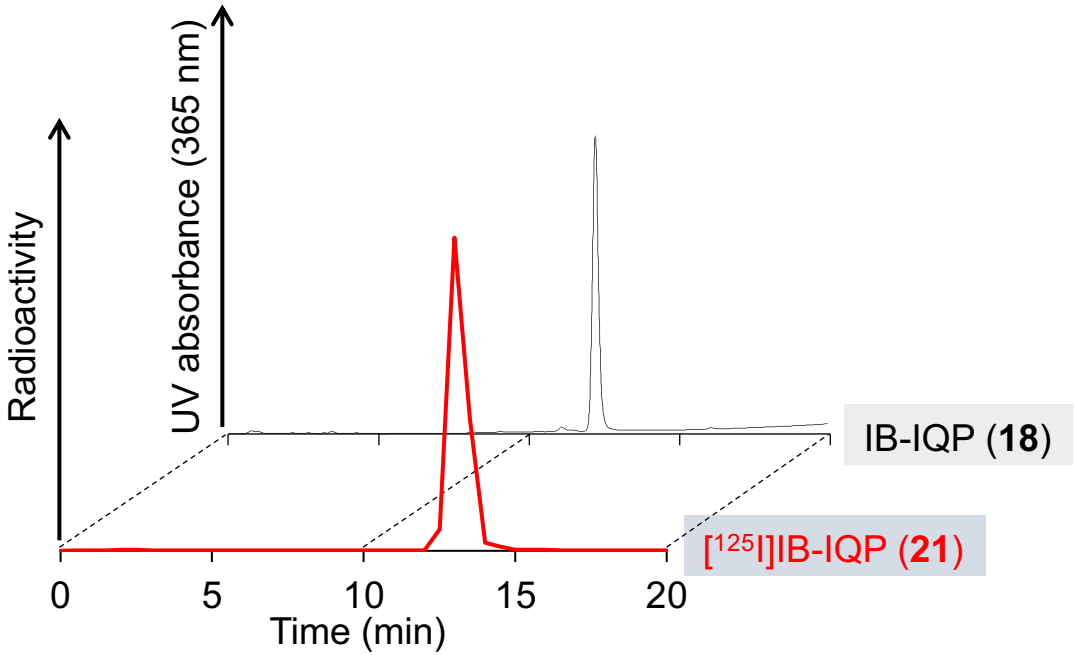
Radiolabeling



19 **21**

(a) [^{125}I]NaI, NCS, acetic acid

Chromatogram of [^{125}I]IB-IQP and IB-IQP



Radiochemical yield: 85.0%

Radiochemical purity: 99.3%

HPLC condition:
Column: 5C$_{18}$-MS-II (4.6 ID x 150 mm)
Mobile phase: (B) 70 – 90%, 0 – 20 min
A) 0.05% TEA in water
B) 0.05% TEA in MeOH
Flow rate: 1.0 mL / min
Temperature: 40 °C

Partition coefficient and stability test

- Partition coefficient of radiotracers

Radiotracer	Log *P* value
[^{125}I]IIQP	2.71 ± 0.03
[^{125}I]IB-IQP	3.19 ± 0.17

$$\boldsymbol{Log\ P} = log\frac{radioactivity\ in\ organic\ layer}{radioactivity\ in\ water\ layer}$$

Organic layer = *n*-octanol
Water layer = 0.1 M phosphate buffer pH 7.4

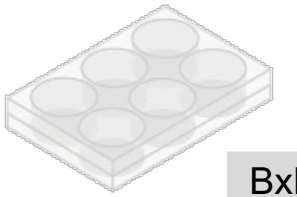
- Stability of radiotracers

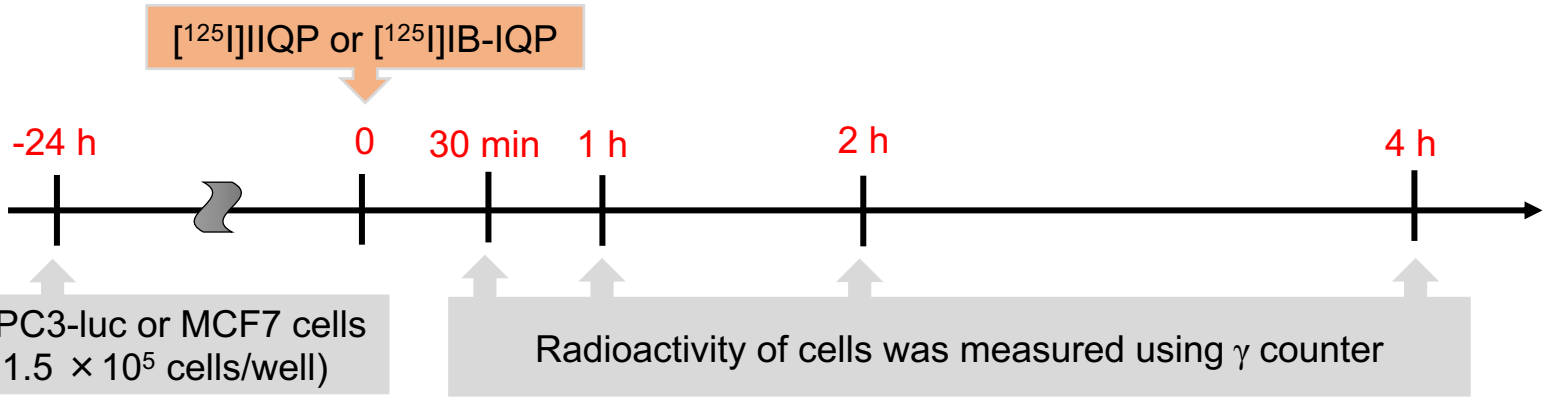
Radiotracer	Purity after 24 h (%)
[^{125}I]IIQP	93.9 ± 0.40
[^{125}I]IB-IQP	94.1 ± 0.70

[^{125}I]IIQP and [^{125}I]IB-IQP were stable in 0.1 M PBS pH 7.4

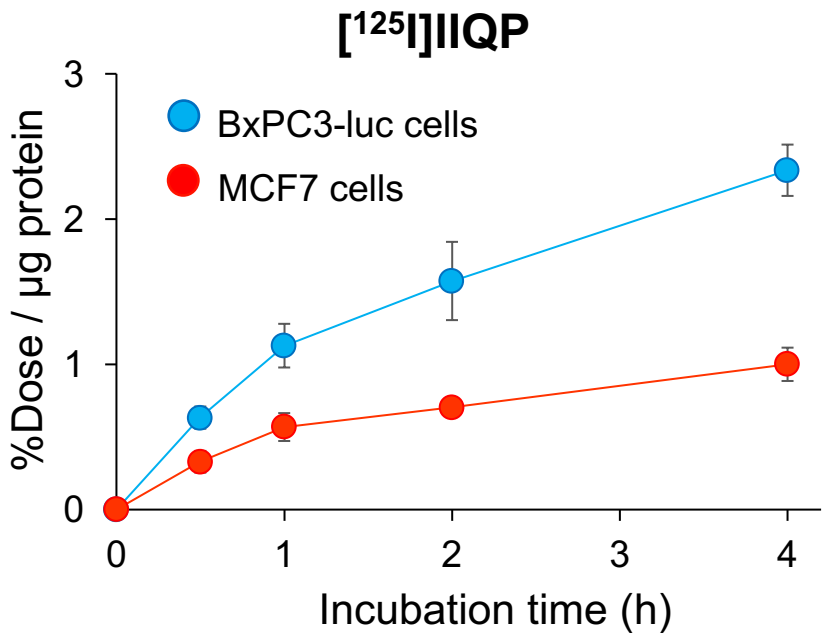
Cell uptake study

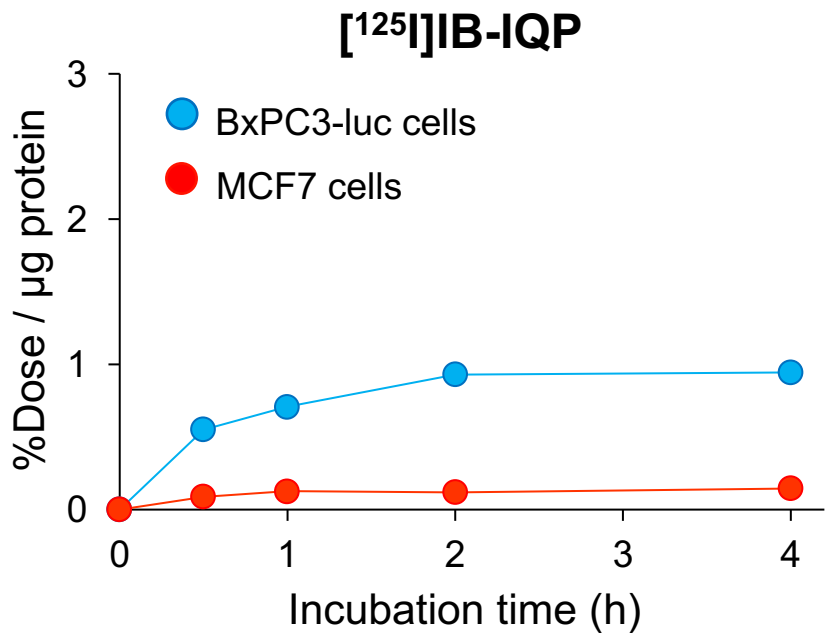
Method





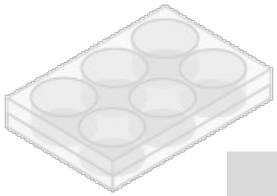
Results

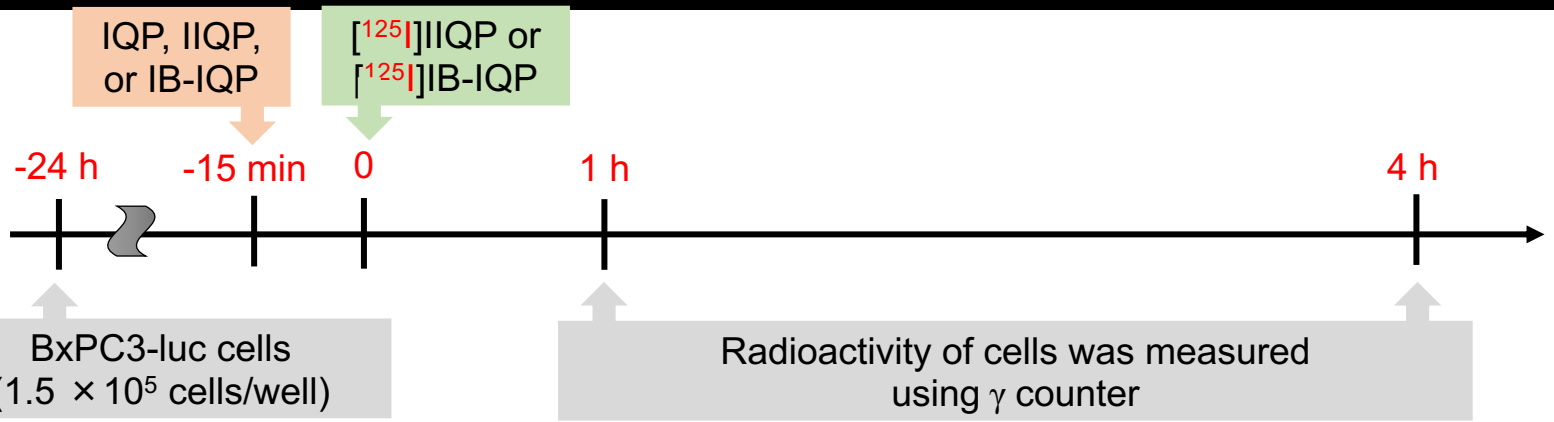




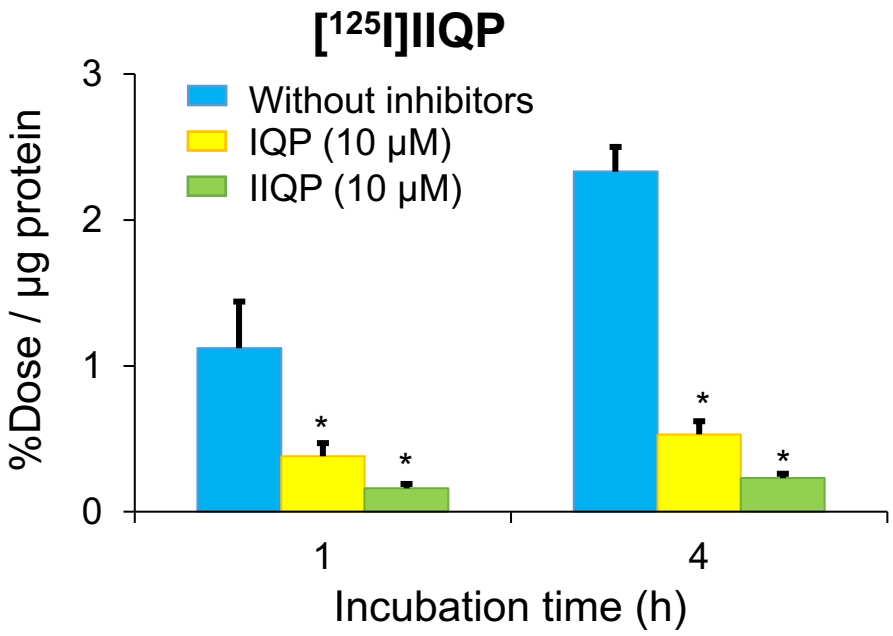
In vitro blocking study

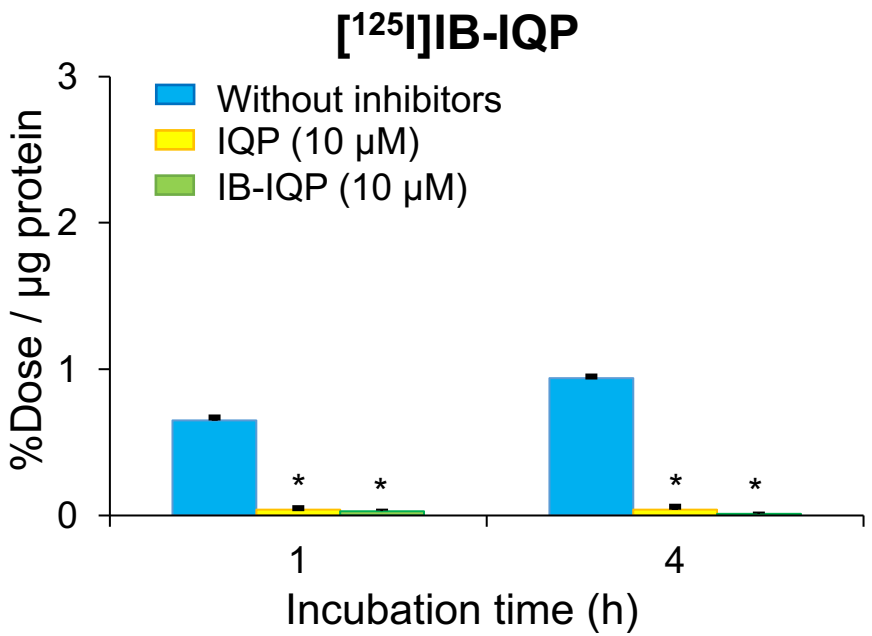
Method





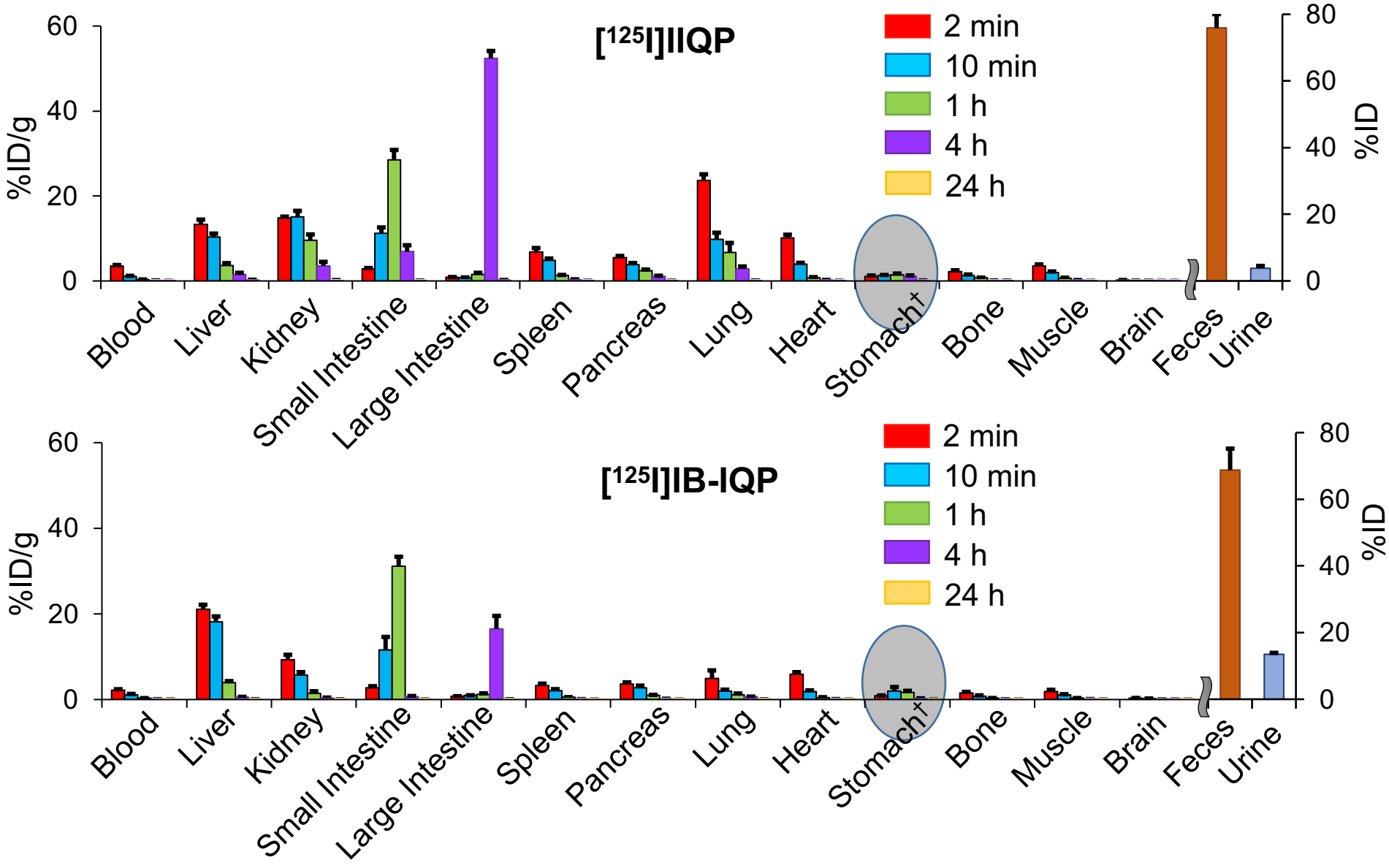
Results





* $p < 0.01$ vs. [125I]IIQP or [125I]IB-IQP

Biodistribution in normal mice (ddY)



†expressed as %ID

Tumor uptake of [^{125}I]IIQP and [^{125}I]IB-IQP in tumor-bearing mice

Method

[^{125}I]IIQP or [^{125}I]IB-IQP

-2 wk | 0 | 1 h

Inoculation of BxPC3-luc cells into nude mice (sc) (5 x 10^6 cells/mouse)

sacrifice

Control group

IQP (i.p.) (40 mg/Kg)

[^{125}I]IIQP

-2 wk | -1 h | 0 | 1 h

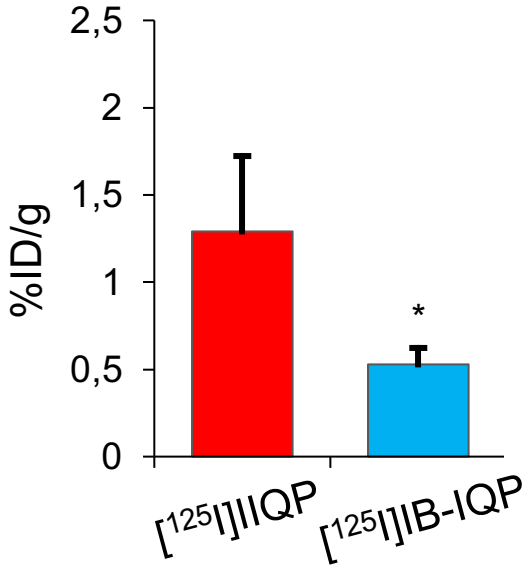
Inoculation of BxPC3-luc cells into nude mice (sc) (5 x 10^6 cells/mouse)

sacrifice

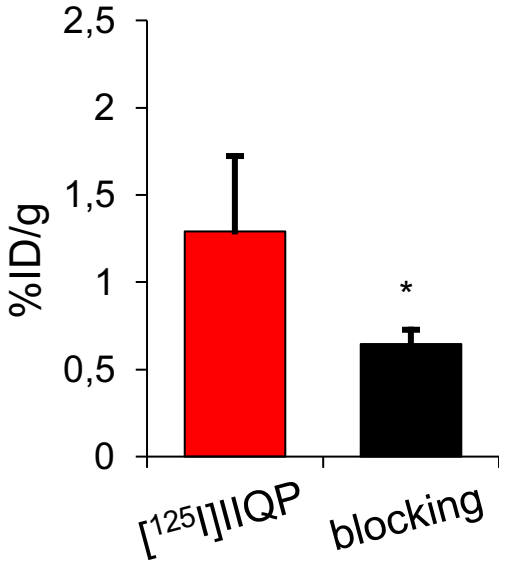
Blocking group

Results

Tumor uptake



In vivo blocking studies



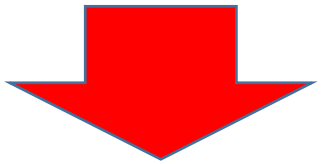
* $p < 0.01$ vs. [^{125}I]IIQP group

Conclusion

1. [^{125}I]IIQP and [^{125}I]IB-IQP were easily synthesized using an iododestannylation reaction under non-carrier added condition with high radiochemical yields (95.0 and 85.0%, respectively) and high purities (>99%).

2. This method can also be used to synthesize other radioiodinated compounds containing benzimidazole-quinoline derivatives.

3. Radioiodinated-IIQP could be more promising for PDGFRβ imaging compared with radioiodinated-IB-IQP.



However, structure modification may be needed to obtain appropriate PDGFRβ-targeted imaging agents.