Design and synthesis of ^{68}Ga-labeled DOTA-conjugated Sstr2-targeting small molecules for imaging neuroendocrine tumor

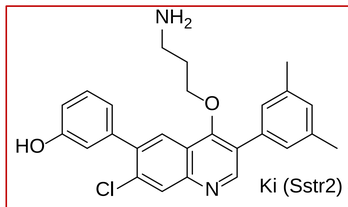
Zhang Z[1], Kuo HT[1], Zhang C[1], Merkens H[1], Bendre S[1], Bénard F[1,2], Lin KS[1,2]

[1] *Department of Molecular Oncology, BC Cancer Research Centre, Vancouver BC, Canada*

[2] *Department of Radiology, University of British Columbia, Vancouver BC, Canada*

OBJECTIVE

Somatostatin receptor subtype 2 (Sstr2) which is overexpressed in neuroendocrine tumors represents an attractive imaging marker and therapeutic target. Radioligands derived from Sstr2-targeting peptides such as DOTATATE have been labeled with therapeutic (Lu-177 and Y-90) radionuclides to treat neuroendocrine tumors. However, most patients do not respond to the treatment of Lu-177 labeled DOTATATE (also called Lutathera). This is because peptide-derived radiotherapeutics are prone to degradation in vivo [Lubberink M et al. J Nucl Med 2020; 61: 1337-1340], leading to suboptimal tumor accumulation and therapeutic efficacy. In this study, we aimed to design and synthesize imaging agents derived from an Sstr2-targeting small-molecule pharmacophore which might be more stable against in vivo degradation.



Ki (Sstr2) = 0.025 nM

Figure 1: Chemical structure of a potent Sstr2-targeting 3,6-diaryl-4-aminoalkoxyquinoline scaffold. .

METHODS

A potent 3,6-diaryl-4-aminoalkoxyquinoline scaffold (Figures 1 and 2) with very high binding affinity to Sstr2 (Ki (Sstr2) = 0.025 nM) was selected and synthesized [Wolkenberg SE et al. J Med Chem 2011; 54: 2351-2358]. Three DOTA-conjugated derivatives (Z06112, Z06111 and Z06110, Figure 3) with -1, neutral and +1 charged linkers were synthesized via solid-phase approach. These three ligands were labeled with Ga-68 in acetate buffer (pH 4) via microwave heating for 1 min. Imaging and biodistribution studies (Table 1 and Figure 4) were carried out at 1-h post-injection in mice bearing Sstr2-expressing AR42J rat pancreatic cancer xenografts.

CONCLUSION

We synthesized three Ga-68 labeled tracers derived from an Sstr2-targeting small-molecule pharmacophore, and successfully evaluated their potential for imaging using a preclinical tumor model. Two of the tracers (Ga-68 labeled Z06112 and Z06111) enabled tumor visualization and showed good tumor-to-muscle contrast ratios. Further investigations on the cause of high blood retention of these tracers are needed to improve their tumor-to-background contrast rations and imaging potentials.

RESULTS

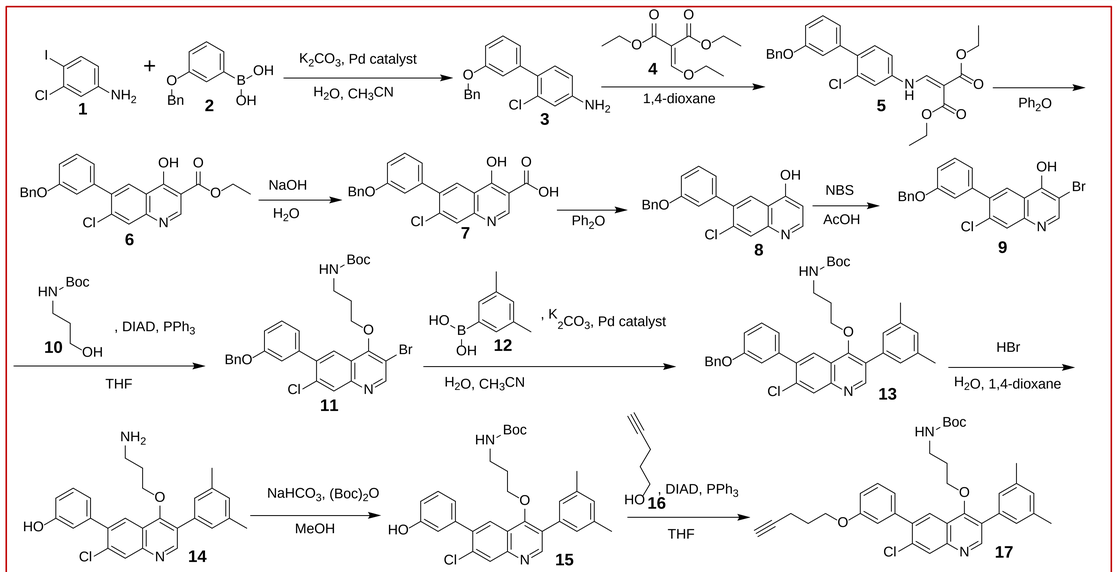


Figure 2: Synthetic scheme for the preparation of the Sstr2-targeting small molecule pharmacophore **17** which can be coupled to solid phase via the Cu(I)-catalyzed click reaction.

Table 1: Biodistribution (%ID/g, 1 h post-injection) of Ga-68 labeled Z06112, Z06111 and Z06110 in mice bearing Sstr2-expressing AR42J tumor xenografts.

	^{68}Ga-Z06112 (n = 3)	^{68}Ga-Z06111 (n = 3)	^{68}Ga-Z06110 (n = 3)
Blood	14.2 ± 1.67	7.78 ± 2.73	3.13 ± 0.36
Urine	29.6 ± 8.34	17.9 ± 9.74	9.69 ± 3.00
Fat	0.66 ± 0.10	0.41 ± 0.14	0.20 ± 0.05
Seminal gland	0.69 ± 0.13	0.50 ± 0.35	0.18 ± 0.02
Testes	1.12 ± 0.01	0.84 ± 0.50	0.24 ± 0.07
Intestines	1.70 ± 0.18	1.26 ± 0.32	0.68 ± 0.06
Stomach	0.68 ± 0.40	0.26 ± 0.15	0.32 ± 0.20
Spleen	3.81 ± 0.87	6.46 ± 2.31	7.57 ± 1.79
Liver	19.4 ± 2.19	30.7 ± 9.76	42.8 ± 4.71
Pancreas	1.00 ± 0.13	0.66 ± 0.14	0.36 ± 0.09
Adrenal gland	3.02 ± 0.57	1.97 ± 0.61	4.22 ± 3.98
Kidney	8.61 ± 0.49	9.04 ± 2.50	8.04 ± 1.39
Lung	17.2 ± 6.54	8.62 ± 1.35	43.2 ± 9.66
Heart	3.00 ± 0.34	2.22 ± 1.09	1.70 ± 0.30
Tumor	3.52 ± 0.14	3.26 ± 1.08	0.77 ± 0.13
Muscle	0.72 ± 0.02	0.40 ± 0.14	0.29 ± 0.03
Bone	1.06 ± 0.27	2.45 ± 0.83	2.89 ± 0.05
Brain	0.26 ± 0.06	0.12 ± 0.03	0.22 ± 0.03
Tail	4.08 ± 1.14	4.36 ± 1.75	4.92 ± 2.32
Tumor/Muscle	4.87 ± 0.27	8.53 ± 3.72	2.60 ± 0.17
Tumor/Blood	0.25 ± 0.04	0.45 ± 0.22	0.24 ± 0.01
Tumor/Kidney	0.41 ± 0.01	0.37 ± 0.13	0.10 ± 0.01

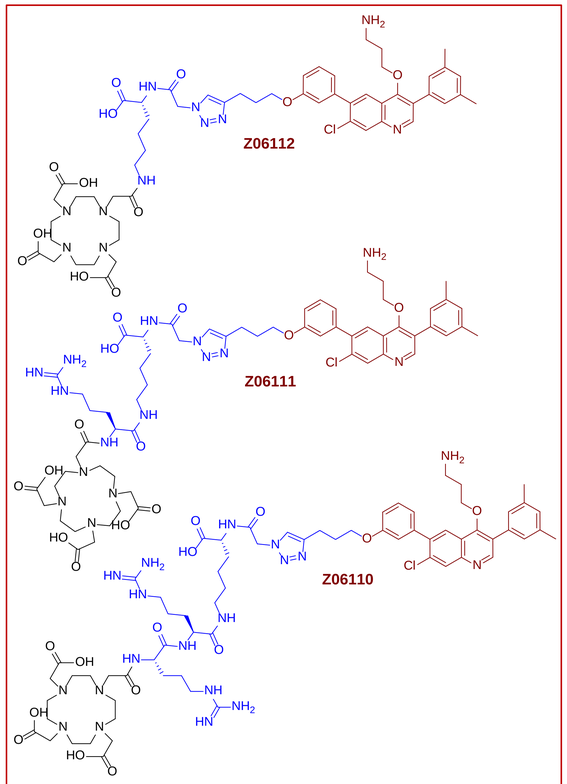


Figure 3: Chemical structures of 3 DOTA-conjugated Sstr2-targeting ligands: Z06112, Z06111 and Z06110.

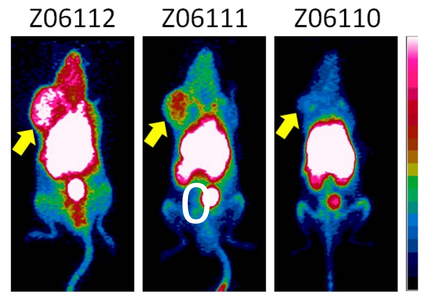


Figure 4: MIP (Maximum Intensity Projection) PET images of Ga-68 labeled Z06112, Z06111 and Z06110 taken at 1 h post-injection in mice bearing Sstr2-expressing AR42J tumor xenografts. The scale of the color bar is 0 – 5 %ID/g and the tumors are indicated by arrows.

AKNOWLEDGMENTS

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