Chempublish Journal
Journal Homepage: online-journal.unja.ac.id/chp
Department of Chemistry
Faculty of Science and Technology
Universitas Jambi
ISSN (Online): ISSN 2503-4588
No. 23/E/KPT/2019

Supplementary Data

Designing L-type Amino Acid Transporter 1-targeting Cancer Theranostic Radiopharmaceuticals: A Molecular Docking Simulation

Holis Abdul Holik[1*], Arifudin Achmad[2], Faisal Maulana Ibrahim[1], Angela Alysia Elaine[1], Jonathan Stefanus[1], B.S. Ari Sudarmanto[3], Achmad Hussein S. Kartamihardja[2]

[1]Department of Pharmaceutical Analysis & Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran; Hegarmanah, Jatinangor, Sumedang 45363, West Java, Indonesia
[2]Department of Nuclear Medicine and Molecular Theranostics, Faculty of Medicine, Universitas Padjadjaran, Bandung 40162, West Java, Indonesia
[3]Laboratory of Medicinal Chemistry, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Gadjah Mada, D.I. Yogyakarta 55281, Indonesia

Abstract

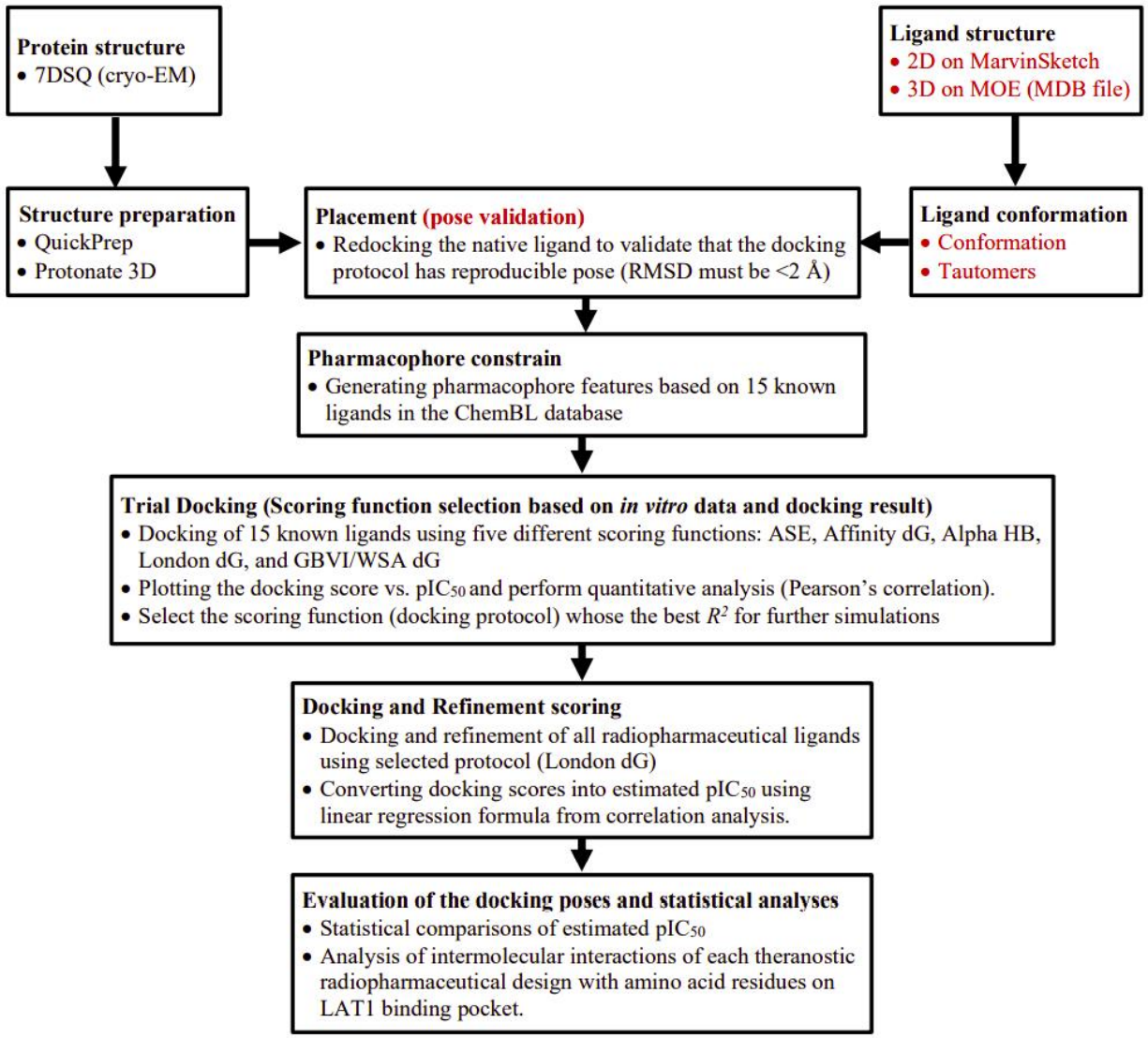
L-type amino acid transporter 1 (LAT1) is a potential pan-cancer theranostic molecular target. The LAT1 inhibitory potencies of eight theranostic radiopharmaceuticals designed based on a potent LAT1 inhibitor ADPB (in vitro predicted pIC_{50} 6.19), were estimated in molecular docking simulations. The designs comprised ADPB as a carrier molecule with/without 6-aminohexanoic acid (Ahx) linker, a chelating agent, and a radiometal (68Ga or 177Lu). JPH203, the most potent LAT1 inhibitor (predicted pIC_{50} 7.22), was utilized as a benchmark compound. A set of known LAT1 ligands (n = 15) were first docked into LAT1 to build the docking protocol with the software Molecular Operating Environment (MOE). Adding a linker improved the LAT1 inhibitory potency of DOTA-conjugated and NODAGA-conjugated ADPB-based theranostic radiopharmaceutical designs. 177Lu-DOTA-Ahx-ADPB has the exceptional LAT1 inhibitory potency (predicted pIC_{50} 51.55 ± 17.06) while 177Lu-DOTA-ADPB, its non-linker counterpart, has LAT1 inhibitory potency significantly higher than the native JPH203. The evaluation of docking poses and quantitative analysis for both 177Lu-DOTA-Ahx-ADPB and 177Lu-DOTA-ADPB have strong bonds with key amino acids on the LAT1 binding pocket, particularly Asn258, Tyr259, and the gating residue Phe252. Our findings provide a quantitative and illustrative understanding of the LAT1 inhibitory potency of LAT1-targeting theranostic radiopharmaceutical designs relevant to the rational design of pan-cancer radiotheranostic drugs.

Keywords: *Chelating agent, LAT1, pan-cancer, Molecular Operating Environment (MOE), theranostic radiopharmaceutical,*

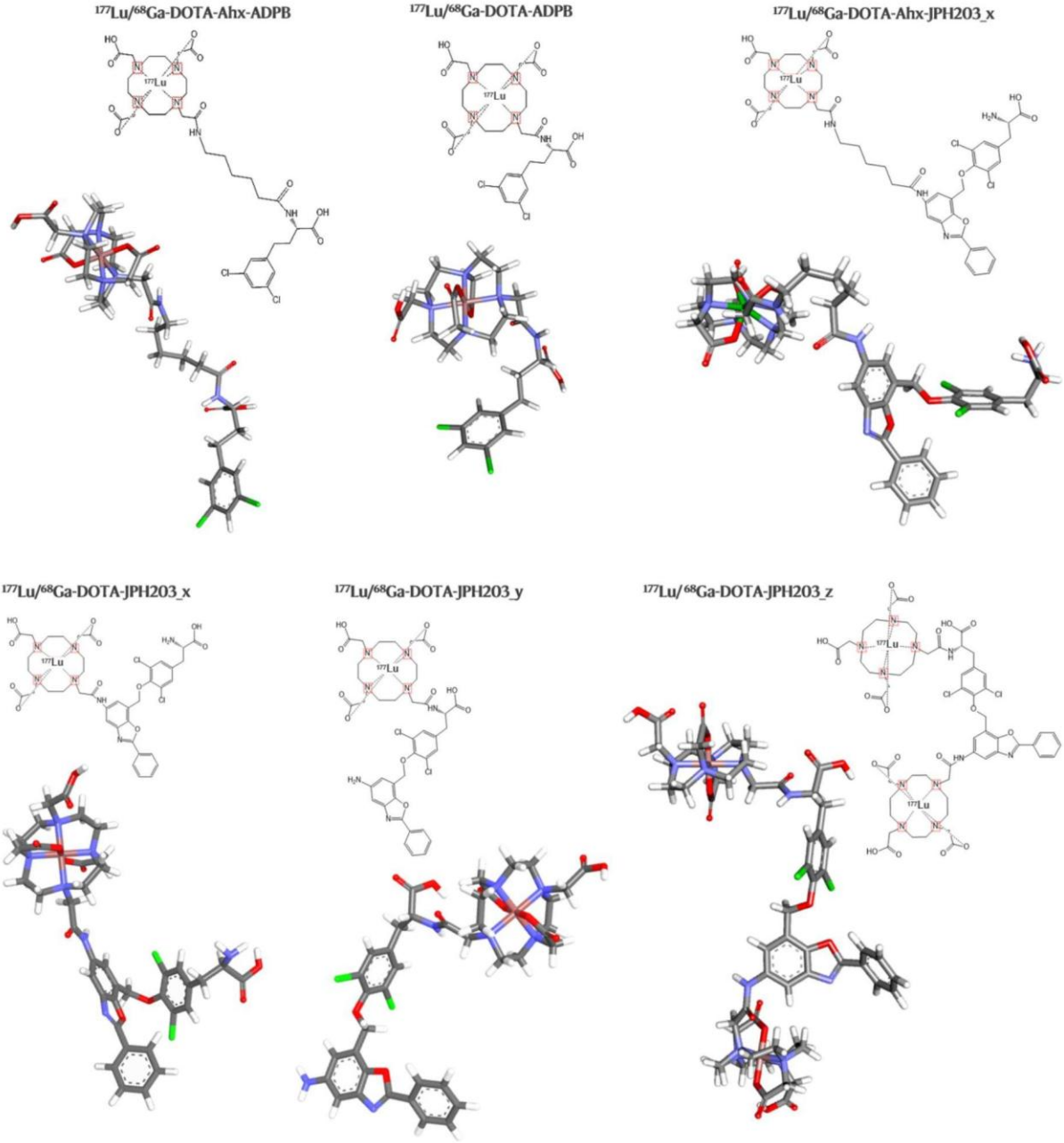
* **Corresponding author**
Email addresses: holis@unpad.ac.id

DOI: https://doi.org/10.22437/chp.v9i2.44633
Received August 28th 2025; **Accepted** October 07th 2025; **Available online** December 31st 2025

Supp. Data S1. The workflow of molecular docking simulation



Supp. Data S2. Representative 2D and 3D drawings of the theranostic radiopharmaceutical design



Supp. Data S3. Mean docking scores and LAT1 inhibitory potency (estimated pIC_{50}) of ADFB-based and JPH203-based theranostic radiopharmaceutical designs

No.	ADPB-based designs	S (kcal/mol)	Estimated pIC_{50}	No.	JPH203-based designs	S (kcal/mol)	Estimated pIC_{50}
1	^{177}Lu-DOTA-Ahx-ADPB	-51.40 ± 16.54	51.55 ± 17.06	1	^{177}Lu-DOTA-Ahx-JPH203_x	-51.42 ± 24.10	51.57 ± 24.86
2	^{177}Lu-DOTA-ADPB	-20.25 ± 7.34	19.42 ± 7.58	2	^{177}Lu-DOTA-Ahx-JPH203_y	-60.65 ± 21.8	61.09 ± 22.49
				3	^{177}Lu-DOTA-Ahx-JPH203_z	-76.64 ± 4.70	77.58 ± 4.85
				4	^{177}Lu-DOTA-JPH203_x	-61.85 ± 13.39	62.32 ± 13.81
				5	^{177}Lu-DOTA-JPH203_y	-63.86 ± 25.46	64.40 ± 26.26
				6	^{177}Lu-DOTA-JPH203_z	-85.89 ± 6.89	87.12 ± 7.11
3	^{68}Ga-DOTA-Ahx-ADPB	-7.69 ± 0.26	6.47 ± 0.27	7	^{68}Ga-DOTA-Ahx-JPH203_x	-10.59 ± 1.65	9.46 ± 1.70
4	^{68}Ga-DOTA-ADPB	-3.98 ± 0.34	2.64 ± 0.35	8	^{68}Ga-DOTA-Ahx-JPH203_y	-14.62 ± 8.76	13.62 ± 9.04
				9	^{68}Ga-DOTA-Ahx-JPH203_z	-13.69 ± 3.44	12.65 ± 3.55
				10	^{68}Ga-DOTA-JPH203_x	-7.59 ± 0.35	6.36 ± 0.36
				11	^{68}Ga-DOTA-JPH203_y	-11.31 ± 4.00	10.20 ± 4.12
				12	^{68}Ga-DOTA-JPH203_z	-18.37 ± 10.11	17.48 ± 10.43
5	^{68}Ga-NOTA-Ahx-ADPB	-6.73 ± 0.28	5.47 ± 0.29	13	^{68}Ga-NOTA-Ahx-JPH203_x	-9.58 ± 0.28	8.41 ± 0.29
6	^{68}Ga-NOTA-ADPB	-6.94 ± 0.37	5.70 ± 0.38	14	^{68}Ga-NOTA-Ahx-JPH203_y	-9.21 ± 0.48	8.04 ± 0.49
				15	^{68}Ga-NOTA-Ahx-JPH203_z	-3.32 ± 1.24	1.96 ± 1.28
				16	^{68}Ga-NOTA-JPH203_x	-7.45 ± 0.13	6.22 ± 0.14
				17	^{68}Ga-NOTA-JPH203_y	-9.11 ± 0.58	7.93 ± 0.59
				18	^{68}Ga-NOTA-JPH203_z	-5.97 ± 2.34	4.69 ± 2.41
7	^{68}Ga-NODAGA-Ahx-ADPB	-8.08 ± 0.30	6.87 ± 0.31	19	^{68}Ga-NODAGA-Ahx-JPH203_x	-9.75 ± 1.06	8.59 ± 1.09
8	^{68}Ga-NODAGA-ADPB	-6.30 ± 0.69	5.03 ± 0.71	20	^{68}Ga-NODAGA-Ahx-JPH203_y	-9.02 ± 0.75	7.83 ± 0.77
				21	^{68}Ga-NODAGA-Ahx-JPH203_z	-8.56 ± 3.60	7.37 ± 3.71
				22	^{68}Ga-NODAGA-JPH203_x	-8.90 ± 0.18	7.71 ± 0.18
				23	^{68}Ga-NODAGA-JPH203_y	-9.25 ± 0.49	8.08 ± 0.51
				24	^{68}Ga-NODAGA-JPH203_z	-8.73 ± 3.53	7.53 ± 3.64

Supp. Data S4. Scoring functions available for molecular docking simulation in MOE

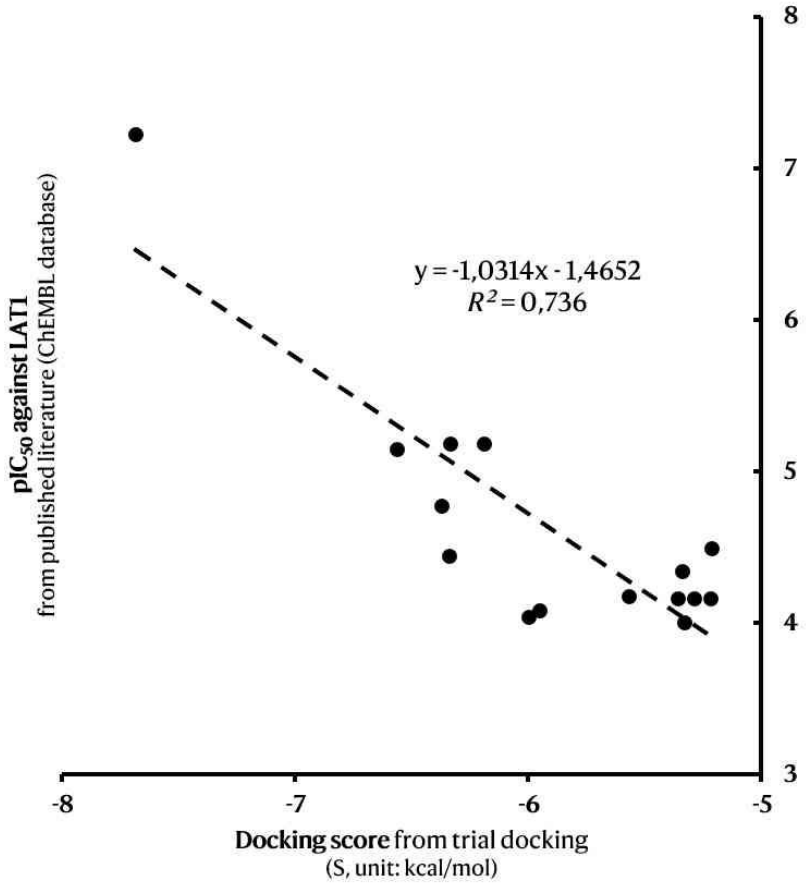
Scoring function	Formula
ASE Based on the Gaussian approximation, depends on the radii of the atoms and the distance between the ligand atom–receptor atom pairs. ASE is proportional to the sum of the Gaussians over all ligand atom–receptor atom pairs.	$\Delta G = R_1 R_2 \, e^{-d^2/2}$ R_1 and R_2 are the radii of the atoms in Å, or are -1.85 Å for alpha spheres. d is the distance between the pair in Å. The proportionality constant has a default value of 0.035 kcal/m
Affinity dG Linear function that calculates the enthalpy contribution to the binding free energy, including terms based on interactions between: 1) H-bond donor–acceptor pairs, 2) hydrophobic and ionic interactions, 3) metal ligation, 4) unfavorable interactions (hydrophobic and polar atoms), and 5) favorable interactions (any two atoms).	$\Delta G = C_{hb} f_{hb} + C_{ion} f_{ion} + C_{mlig} f_{mlig} + C_{hh} f_{hh} + C_{hp} f_{hp} + C_{aa} f_{aa}$ f are fractional count of atomic contacts of specific types C are coefficients that weight the term contributions to the affinity estimate. The individual terms are: *hb* is interaction between hydrogen bond donor-acceptor pairs. *ion* is interactions between charged groups. *mlig* is interactions between Nitrogens/Sulfurs and transition metals are assumed to be metal ligation interactions. *hh* is hydrophobic interactions, e.g., between alkane carbons (generally favorable) *hp* is interactions between hydrophobic and polar atoms (generally unfavorable). *aa* is weak interaction between any two atoms, and generally favorable.
Alpha HB Linear combination of two terms: (1) the geometric fit of the ligand to the binding site taking into account the attraction and repulsion depending on the distance between the atoms; and (2) H-bonding effects.	**First term:** Combination of attractive components and repulsive components. The attractive component is summed over atoms in the ligand. Each ligand atom (within 3 Å of an alpha sphere center) contributes $Ae^{-d^2/2}$ while d is the distance from the ligand atom to the nearest alpha sphere center, A = -0.6845 The repulsive component is summed over all pairs of atomic overlap between the ligand and the receptor. For each pair of overlap, the contribution is between 0 and 1 depending on the severity of the overlap. **Second term:** For non-sp3 donors and acceptors: If the site is occupied by a favorable atom, there is a score of -2 (negative means favorable). If it is occupied by some other ligand atom, there is a score of +1. For sp3 donors and acceptors, all favorable atoms within 3.5 Å contribute a score of -1 while all other atoms contribute +1. Metals in the receptor are treated as acceptors but with a three-fold effect.
London dG Estimation of the free binding energy of the ligand, counting for the average gain or loss of rotational and translational entropy; the loss of flexibility of the ligand; the geometric imperfections of H-bonds and metal ligations compared to the ideal ones; and the desolvation energy of atoms.	$\Delta G = c + E_{\text{flex}} + \sum_{h-bonds} c_{HB} f_{HB} + \sum_{m-lig} c_M f_M + \sum_{atoms\ i} \Delta D_i$ where c is the average gain/loss of rotational and translational entropy; E_{flex} is the energy due to the loss of ligand flexibility (from ligand topology only); f_{HB} is geometric imperfections of hydrogen bonds and takes a value in [0,1]; c_{HB} is the energy of an ideal hydrogen bond; f_M measures geometric imperfections of metal ligations and takes a value in [0,1]; c_M is the energy of an ideal metal ligation; and ΔD_i is the desolvation energy of atom i.
GBVI/WSA dG Estimation of the free energy of binding of the ligand taking into account the weighted terms for the Coulomb energy, solvation energy, and van der Waals contributions.	$\Delta G \approx c + \alpha \left[\frac{2}{3}(\Delta E_{Coul} + \Delta E_{sol}) + \Delta E_{vdW} + \beta \Delta SA_{Weighted}\right]$ where c is the average gain/loss of rotational and translational entropy. α, β are constants which were determined during training (along with c and are forcefield-dependent. If not using an AMBER forcefield, the parameters will be set by default to the MMFF trained parameters. E_{coul} is the coulombic electrostatic term which is calculated using currently loaded charges, using a constant dielectric of εi=1. E_{sol} is the solvation electrostatic term which is calculated using the GB/VI solvation model. E_{vdW} is the van der Waals contribution to binding. $SA_{weighted}$ is the surface area, weighted by exposure. This weighting scheme penalizes exposed surface area.

Taken from MOE user manual (#ref).

Supp. Data S5. Known LAT1 ligands

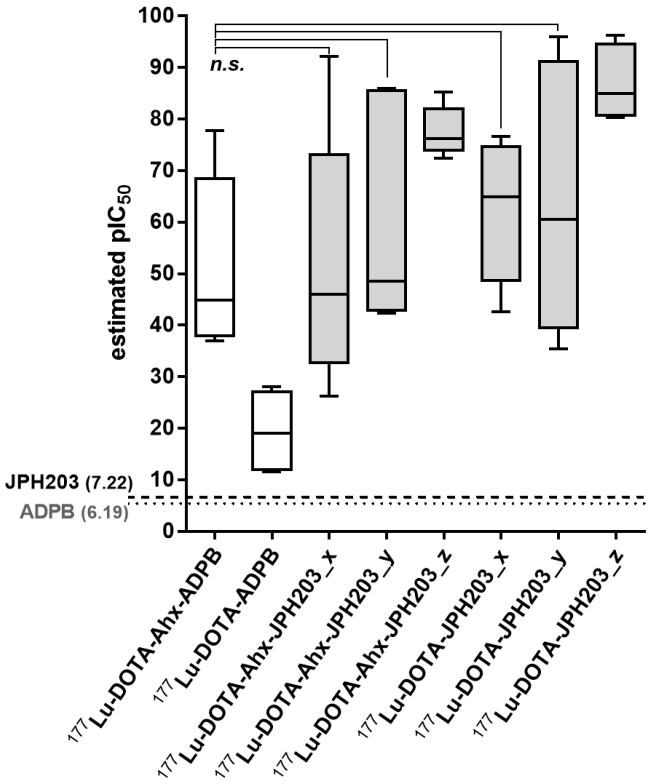
pIC_{50} (experimental values)	IUPAC name	Other name	S (docking score)
7,22	(2S)-3-[4-[(5-amino-2-phenyl-1,3-benzoxazol-7-yl)methoxy]-3,5-dichlorophenyl]-2-azaniumylpropanoate	JPH203	-7,68
5,14	(2S)-2-azaniumyl-3-(3-benzylphenyl)propanoate	compound 28/69	-6,56
5,18	(2S)-2-azaniumyl-3-(3-phenylphenyl)propanoate	-	-6,33
4,16	(2S)-2-azaniumyl-3-phenylpropanoate	L-phenylalanine zwitterion	-5,36
4,34	(2R)-2-azaniumyl-3-phenylpropanoate	D-phenylalanine zwitterion	-5,34
4,17	(2S)-2-azaniumyl-3-(4-hydroxyphenyl)propanoate	-	-5,57
4,16	(2S)-2-azaniumyl-3-pyridin-3-ylpropanoate	-	-5,22
5,18	(2S)-2-azaniumyl-3-(3-phenylphenyl)propanoate	-	-6,19
4,08	(2S)-2-azaniumyl-3-[3-(hydroxymethyl)phenyl]propanoate	-	-5,95
4,04	(2S)-3-(3-acetylphenyl)-2-azaniumylpropanoate	compound 77	-6,00
4,44	(2S)-2-azaniumyl-3-(3-methoxycarbonylphenyl)propanoate	compound 79	-6,34
4,77	(2S)-2-azaniumyl-3-[3-[(2-methylpropan-2-yl)oxycarbonyl]phenyl]propanoate	compound 81	-6,37
4,49	(2R)-2-azaniumyl-3-[3-[2-(3,4-dihydroxyphenyl)ethylcarbamoyl]phenyl]propanoate	DOPA-AMD	-5,21
4,00	(2S)-2-azaniumyl-3-(3,4-dihydroxyphenyl)propanoate	Levodopa	-5,33
4,16	(2S)-2-azaniumyl-3-pyridin-3-ylpropanoate	-	-5,29

Supp. Data S6. Correlation analysis between established LAT1 inhibition pIC_{50} of known ligands and their docking scores obtained in trial docking using London dG scoring function



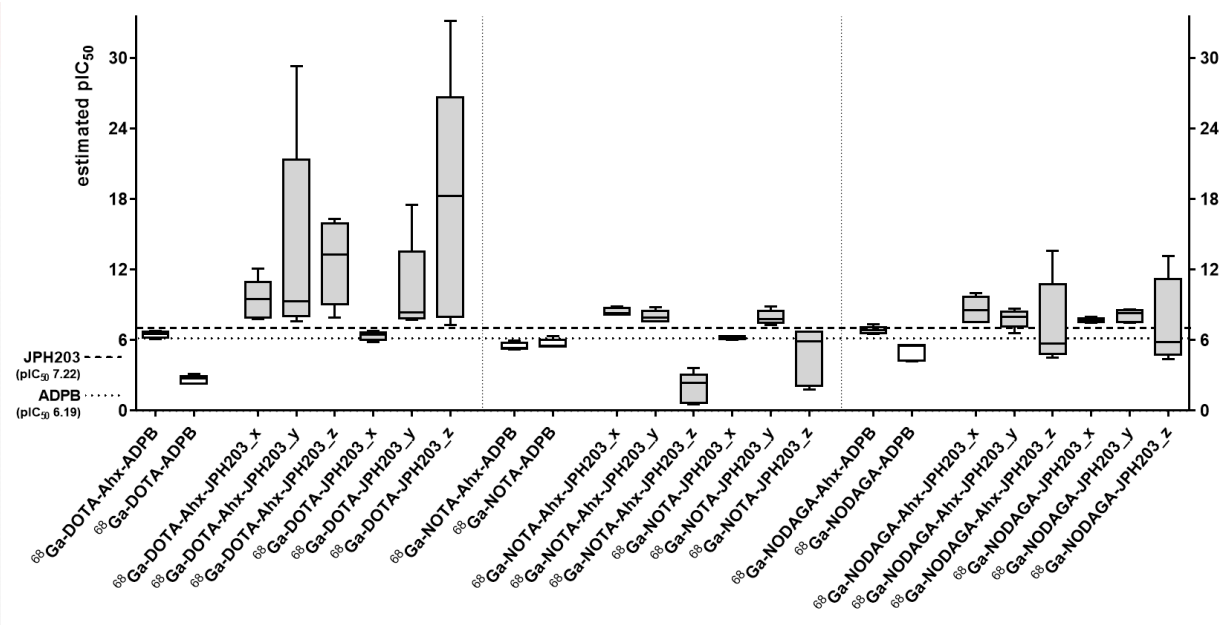
Supp. Data S7. Estimated pIC_{50} of ADPB-based and JPH203-based theranostic radiopharmaceutical designs

Figure S7a



Estimated pIC_{50} of ADPB-based and JPH203-based theranostic radiopharmaceutical designs containing ^{177}Lu radiometal, n = 5 for each design, n.s. statistically not significant.

Figure S7b



Estimated pIC_{50} of ADPB-based and JPH203-based theranostic radiopharmaceutical designs containing ^{68}Ga radiometal, n = 5 for each design, n.s. statistically not significant.

Supp. Data S8. Statistical comparison of LAT1 inhibitory potencies among ADPB-based theranostic radiopharmaceutical designs, native ADPB, and native JPH203.

	Compared each other, *P* value*	Compared to native ADPB (6.19), *P* value	Compared to native JPH203 (7.22), *P* value
^{177}Lu-DOTA-Ahx-ADPB	0.0049	Higher, 0.0040	Higher, 0.0044
^{177}Lu-DOTA-ADPB		Higher, 0.0175	Higher, 0.0227
^{68}Ga-DOTA-Ahx-ADPB	<0.0001	Equal, 0.0823 (*n.s.*)	Lower, 0.0035
^{68}Ga-DOTA-ADPB		Lower, <0.0001	Lower, <0.0001
^{68}Ga-NOTA-Ahx-ADPB	Equal, 0.3095	Lower, 0.0053	Lower, 0.0002
^{68}Ga-NOTA-ADPB		Lower, 0.0441	Lower, 0.0009
^{68}Ga-NODAGA-Ahx-ADPB	0.0079	Higher, 0.0079	Equal, 0.0626 (*n.s.*)
^{68}Ga-NODAGA-ADPB		Lower, 0.0216	Lower, 0.0023

n = 5 in each design. *n.s.* statistically not significant
*When compared each other, all ADPB-based designs containing Ahx linker showed significantly higher LAT1 inhibitory potency compared to their counterparts, except ^{68}Ga-NOTA-Ahx-ADPB.