Supporting Information

Synthesis, Radiosynthesis, and Biological Evaluation of Carbon-11 and Fluorine-18 Labeled Reboxetine Analogs: Potential Positron Emission Tomography Radioligands for in Vivo Imaging of the Norepinephrine Transporter

Fanxing Zeng,[†] Jiyoung Mun,[†] Nachwa Jarkas,[†] Jeffrey S. Stehouwer,[†] Ronald J. Voll,[†] Gilles D. Tamagnan,[‡] Leonard Howell,[⊥] John R. Votaw,[†] Clinton D. Kilts,[§] Charles B. Nemeroff [§] and Mark M. Goodman[†,*]

[†] Department of Radiology.
[§] Department of Psychiatry and Behavioral Sciences.
[⊥] Yerkes Regional Primate Research Center.
[#] Institute for Degenerative Diseases.

Table of Contents

Rodent Biodistribution Studies

Whole-body biodistribution study of [^{11}C]**1** expressed as percent dose per gram in selected tissues was performed in Sprague-Dawley rats by administration of approximately 300 μCi of [^{11}C]**1**. The time-course concentration of [^{11}C]**1** in the blood and in different regions is shown is Table S1. [^{11}C]**1** showed moderate initial brain uptake with highest uptake of radioactivity of 0.90% dose/g at 5 min after injection and then a gradual decrease with time. The high uptake was observed in the lung, heart, spleen, and kidney followed by a rapid clearance.

Table S1. Whole-body Biodistribution of [^{11}C]**1** in Sprague-Dawley Rats[a]

	5 min	15 min	30 min	60 min
blood	0.13 ± 0.01	0.05 ± 0.01	0.05 ± 0.03	0.04 ± 0.01
heart	3.43 ± 0.48	1.49 ± 0.22	1.07 ± 0.33	0.62 ± 0.11
lung	15.3 ± 4.3	6.92 ± 1.95	3.63 ± 1.47	1.98 ± 1.15
kidney	2.66 ± 0.51	0.85 ± 0.11	0.56 ± 0.13	0.31 ± 0.02
spleen	3.50 ± 0.84	1.79 ± 0.16	1.13 ± 0.36	0.49 ± 0.19
liver	0.28 ± 0.61	0.77 ± 0.14	0.46 ± 0.15	0.29 ± 0.07
muscle	0.25 ± 0.08	0.22 ± 0.07	0.22 ± 0.04	0.22 ± 0.09
testis	0.18 ± 0.02	0.18 ± 0.03	0.19 ± 0.03	0.15 ± 0.04
pancreas	1.59 ± 0.41	0.83 ± 0.11	0.77 ± 0.21	0.63 ± 0.03
brain	0.90 ± 0.13	0.72 ± 0.06	0.55 ± 0.07	0.25 ± 0.04
bone	0.48 ± 0.20	0.37 ± 0.03	0.20 ± 0.10	0.17 ± 0.02

[a]Values are reported as the mean %ID/gram tissue ± standard deviation (n = 5).

Table S2. Elemental analysis of compounds.

Compound	Formula	Calcd.	Found
1	$C_{18}H_{21}O_2N$	C, 76.29; H, 7.47; N, 4.94	C, 76.07; H, 7.49; N, 4.83
2	$C_{19}H_{22}FNO_2$	C, 72.36; H, 7.03; N, 4.44	C, 72.24; H, 7.02; N, 4.36
3	$C_{20}H_{24}FNO_2$	C, 72.92; H, 7.34; N, 4.25	C, 72.96; H, 7.40; N, 4.04
4	$C_{18}H_{21}ONS$	C, 72.20; H, 7.07; N, 4.68	C, 72.14; H, 7.04; N, 4.37

Experimental Section

Rodent Biodistribution Studies. Tissue distribution studies were performed in male Sprague-Dawley rats (200-250 g) after intravenous injection of [^{11}C]**1** in 300 μL of 10% ethanol/saline. The animals were allowed food and water ad libitum before the experiments. Following anesthesia induced with an intramuscular injection of 0.1 mL/100 g of a 1:1 ketamine (500 mg/mL): xylazine (20 mg/mL) solution, the radiolabeled solutions were injected into each of the rat subgroups via tail vein catheter. Groups of five rats were sacrificed at 5, 15, 30, and 60 minutes after injection of the dose. The rats were dissected, and selected tissues were weighed and counted along with dose standards in a Packard Cobra II Auto-Gamma Counter. The raw counts were decay-corrected to a standard time and normalized as the percent of the total injected dose per gram of tissue (%ID/g).