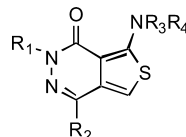
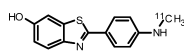


# Imaging Probes of Tau Pathology

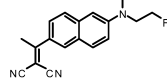
Gerard Rosse\*

Structure Guided Chemistry, Dart Neuroscience LLC, 7473 Lusk Boulevard, San Diego, California 92121, United States, and Adjunct Associate Professor, Department of Pharmacology and Physiology, College of Medicine, Drexel University, New College Building, 245 North 15th Street, Philadelphia, Pennsylvania 19102, United States

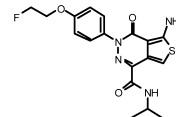
**Title:** Imaging Probes of Tau Pathology  
**Patent/Patent Application Number:** WO 2013090497 A1  
**Priority Application:** US 2011-57915P  
**Inventors:** Jones, C.; Glaser, M. E.; Wynn, D.; Nairne, J.; Mokkapatil, U. P.; Newington, I. M.; Rangaswamy, C.; Jose, J.; Johansson, S.  
**Assignee Company:** GE Healthcare Limited, UK; Medi-Physics, Inc.  
**Disease Area:** Alzheimer's Disease  
**Biological Target:** Tau aggregates  
**Summary:** The patent application claims pyridazinone derivatives as imaging probes of Tau pathology in Alzheimer's disease (AD). The compounds of the present invention may be used for PET or SPECT imaging. Compounds **38** and **105** showed selectivity for tau<sup>+</sup> neurofibrillary tangles (NFTs) over  $\beta$ -amyloid (A $\beta$ )<sup>+</sup> plaques when tested at lower concentration.

**Important Compound Classes:****Key Structures:**

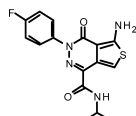
PIB



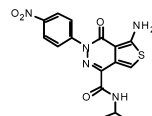
FDDNP



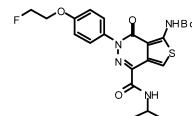
Compound 38



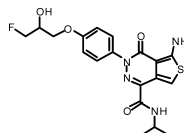
Compound 14



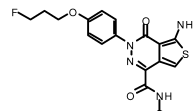
Compound 105



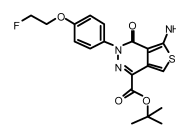
Compound 64



Compound 59



Compound 61



Compound 104

**Recent Review Articles:** Savelieff, M. G.; Lee, S.; Liu, Y.; Lim, M. H. Untangling amyloid- $\beta$ , tau, and metals in Alzheimer's disease. *ACS Chem. Biol.* **2013**, *8* (5), 856–865.

**Biological Assays:** Tissue binding assays: the binding of compounds to NFTs and (A $\beta$ )<sup>+</sup> plaques in human AD tissues were evaluated based on fluorescence.

In vivo cold biodistribution: plasma and brain concentration test compounds was measured after i.p. dosing

In vivo biodistribution with radiolabeled compounds: radioactivity of organs, tissues, and blood was measured after i.v. administration of [<sup>18</sup>F]-radiolabeled compounds

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## Pharmacological Data:

Table 1: Binding to NFTs and (A $\beta$ )<sup>+</sup> plaques in human tissues

Compound	Concentration (mM)	NFTs	Plaques
<b>PIB</b>	100	+++	+++
	10	+	++
	1	-	++
<b>FDDNP</b>	100	+++	+++
	10	++	++
	1	+	+
<b>38</b>	100	+++	++
	10	++	+
	1	+	-
<b>14</b>	100	+	+
	10	-	-
	1	-	-
<b>105</b>	100	++	++
	10	+	-
	1	-	-
<b>64</b>	100	-	-
<b>59</b>	100	-	-
<b>61</b>	100	-	-
<b>104</b>	100	-	-

+++ = intense staining, ++ = moderate staining, + weak staining, - no staining

Table 2: Cold biodistribution in rat

Compound	Brain uptake %compound/ p.i. (min)				Clearance ratio 2:30 min
	2	10	30	60	
<b>38</b>	0.28	0.081	0.021	0.011	13.3

Table 3: Biodistribution of radiolabeled compounds in mouse

Compound	Brain uptake %compound/ p.i. (min)				Clearance ratio 2:30 min
	2	10	30	60	
[ <sup>18</sup> F]- <b>38</b>	6.50	3.26	2.83	2.35	2.3
[ <sup>18</sup> F]- <b>61</b>	9.84	5.77	3.46	1.51	2.8

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### Notes

The authors declare no competing financial interest.