

Appendix 12 Hematology (TK satellite group) B131138

Sex: Male Day(s) Relative to Start Date

25 mg/kg	Hematology													
	Red Blood Cell Count (10 ⁶ /μL)	Hemoglobin conc. (g/dL)	Hematocrit (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet Count (10 ³ /μL)	Reticulocyte (%)	PT (sec)	APTT (sec)	White Blood Cell Count (10 ³ /μL)	Lymphocyte (%)	Neutrophil (%)	Eosinophil (%)
	29	29	29	29	29	29	29	29	29	29	29	29	29	29
20304	7.26	13.6	38.1	52.5	18.7	35.7	1497	3.66	9.1	12.5	14.32	50.0	47.0	0.4

Appendix 12 Hematology (TK satellite group) B131138

Sex: Male Day(s) Relative to Start Date

25 mg/kg	Hematology						
	Basophil	Monocyte	Lymphocyte	Neutrophil	Eosinophil	Basophil	Monocyte
	(%)	(%)	(10 ³ /μL)				
	29	29	29	29	29	29	29
20304	0.0	2.6	7.16	6.73	0.06	0.00	0.37

Appendix 13

Blood Chemistry (TK satellite group)

B131138

Sex: Male Day(s) Relative to Start Date

25 mg/kg	Blood Chemistry													
	ASAT (U/L)	ALAT (U/L)	LDH (U/L)	Gamma GT (U/L)	ALP (U/L)	Creatine Kinase (U/L)	Total Bilirubin (mg/dL)	Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Glucose (mg/dL)	Total Cholesterol (mg/dL)	Phospholipid (mg/dL)	Triglyceride (mg/dL)	Total Protein (g/dL)
	29	29	29	29	29	29	29	29	29	29	29	29	29	29
20304	112	33	242	1	533	174	0.1	16.0	0.2	97	49	73	21	5.7

Appendix 13 Blood Chemistry (TK satellite group)

B131138

Sex: Male Day(s) Relative to Start Date

25 mg/kg	Blood Chemistry													
	A/G Ratio	Albumin (%)	Alpha1 Globulin (%)	Alpha2 Globulin (%)	Beta Globulin (%)	Gamma Globulin (%)	Albumin (g/dL)	Alpha1 Globulin (g/dL)	Alpha2 Globulin (g/dL)	Beta Globulin (g/dL)	Gamma Globulin (g/dL)	Ca (mg/dL)	Inorganic Phosphorus (mg/dL)	Na (mmol/L)
	29	29	29	29	29	29	29	29	29	29	29	29	29	29
20304	0.62	38.3	22.3	11.3	23.1	5.0	2.2	1.3	0.6	1.3	0.3	9.5	8.3	146

Sex: Male Day(s) Relative to Start Date

25 mg/kg	Blood Chemistry	
	K	Cl
	(mmol/L)	(mmol/L)
	29	29
20304	4.6	106

Appendix 14 Organ Weight (TK satellite group) B131138

Sex: Male Day(s) Relative to Start Date

25 mg/kg	Organ Weight (Rat)													
	Final Body Weight (g)	Brain (g)	Brain Ratio (%)	Pituitary (mg)	Pituitary Ratio ($\times 10^{-3}\%$)	Thyroids (mg)	Thyroids Ratio ($\times 10^{-3}\%$)	Thymus (mg)	Thymus Ratio ($\times 10^{-3}\%$)	Submand. GLs (g)	Submand. GLs Ratio (%)	Lungs (g)	Lungs Ratio (%)	Heart (g)
	29	29	29	29	29	29	29	29	29	29	29	29	29	29
20304	412.0	1.97	0.48	15.8	3.8	24.6	6.0	308	74.8	0.69	0.17	1.73	0.42	1.31

Appendix 14 Organ Weight (TK satellite group) B131138

Sex: Male Day(s) Relative to Start Date

25 mg/kg	Organ Weight (Rat)												
	Heart Ratio (%)	Liver (g)	Liver Ratio (%)	Spleen (g)	Spleen Ratio (%)	Kidneys (g)	Kidneys Ratio (%)	Adrenals (mg)	Adrenals Ratio ($\times 10^3$ -3%)	Testes (g)	Testes Ratio (%)	Prostate (g)	Prostate Ratio (%)
	29	29	29	29	29	29	29	29	29	29	29	29	29
20304	0.32	8.91	2.16	0.85	0.21	3.11	0.75	63.2	15.3	3.72	0.90	0.46	0.11

SEX: MALE

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GROUP 5 5 5 5 5 6 6 6 7 7 7
REMOVAL REASON F F F F F F F D F F F
ANIMAL 2 2 2 2 2 2 2 2 2 2 2
NUMBER 0 0 0 0 0 0 0 0 0 0 0
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        0 0 0 0 0 0 0 0 0 0 0
        1 2 3 4 5 1 2 4 5 1 3 4 5

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Necropsy Findings; ..... + + + + + + + + + + +
Present ..... P P P P P P P P P
Absent ..... P P P P P . . . . .

Administered Site; ..... + + + + + + + + +
Nodule ..... P P P . P P P P
Hematoma ..... P . . . . .

Abdominal Cavity; ..... + . + . +
Increase; abdominal fluid ..... P . . . .
Adhesion; multiple organs; hematoma ..... P . . . .
Adhesion; multiple organs; nodule ..... P . P

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SEX: FEMALE

GROUP 7
REMOVAL REASON D

ANIMAL 6
NUMBER 0
3
0
4

.....

Necropsy Findings; +
 Present P

Administered Site; +
 Nodule P

Abdominal Cavity; +
 Increase; abdominal fluid P
 Adhesion; multiple organs; nodule P

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Key Page

Group Code	Description
5	1 mg/kg
6	10 mg/kg
7	25 mg/kg

Removal Reason Code	Description
D	Death
F	Scheduled sacrifice

Tissue Result Code	Description
N	N.V.L
.	Not Recorded
+	Tissue Observation Present
X	Not Examined

Grade Code	Description
.	not recorded
#	duplicate
P	present - no grade or classification

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11. [^{14}C]P092 マレイン酸塩の合成

Synthesis of [¹⁴C]P092 maleate

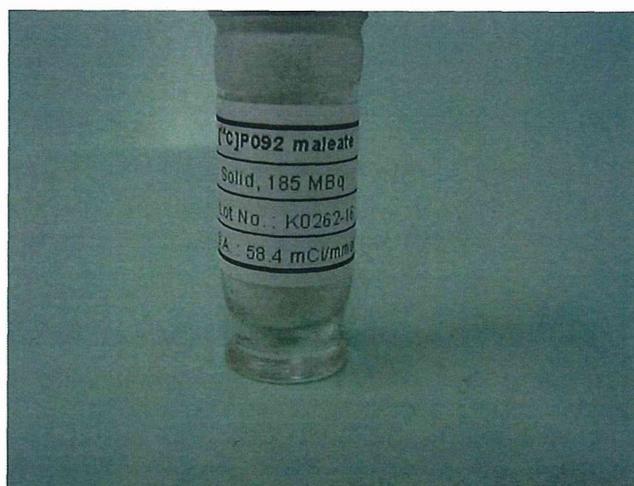
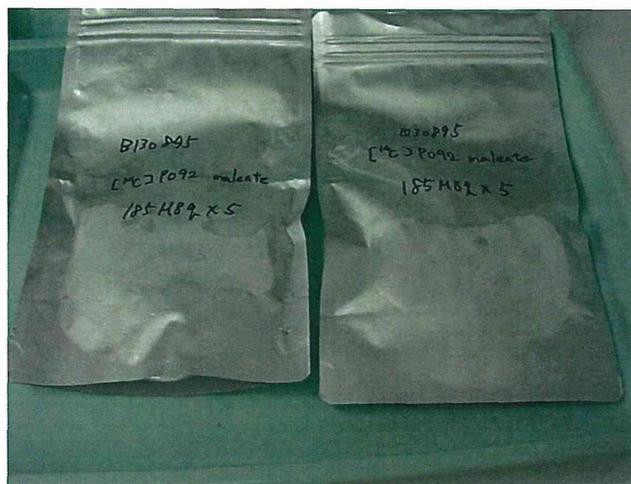
(Study No.:B130895)

Mitsubishi Chemical Medience Corporation

Head office: 4-2-8, Shibaura, Minato-ku, Tokyo
Kashima Laboratory: 14-1 Sunayama, Kamisu-shi, Ibaraki

Total 11 pages

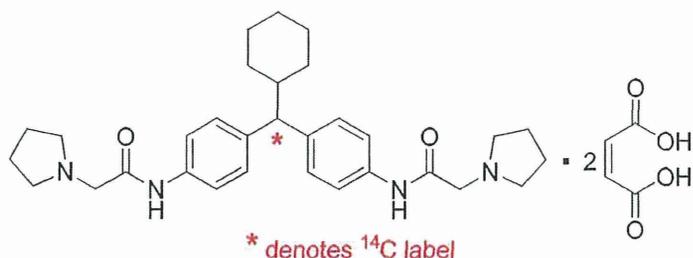
Pictures: [¹⁴C]P092 maleate



CERTIFICATE OF ANALYSIS

(non-GMP, For Research Use Only)

Project No. C-0188



PRODUCT NAME	: [14C]P092 maleate
MOLECULAR FORMULA	: ¹⁴ C ₁ C ₃₈ H ₅₀ N ₄ O ₁₀
MOLECULAR WEIGHT	: 736.70 (at this specific activity)
LOT NUMBER	: K0262-16
DATE OF ANALYSIS	: February 21, 2014
SPECIFIC ACTIVITY	: 58.4 mCi/mmol by LSC
CHEMICAL PURITY	: 98.2% by UV-HPLC
RADIOCHEMICAL PURITY	: 98.5% by HPLC on-line β-RAM & Laura 4
PHYSICAL DESCRIPTION	: White Solid
PACKAGING	: 1850 MBq (50 mCi) in screw-capped 10 vials (185 MBq x 10 vials)
STORAGE	: Store at -80 °C in the absence of moisture, light and air

SPECTROSCOPIC DATA:

¹H Nuclear Magnetic Resonance Spectroscopy

Instrument : Varian 400 MHz

Solvent : D₂O

APCI Mass Spectroscopy

Instrument : Thermo LCQ-Fleet

CHROMATOGRAPHIC DATA:

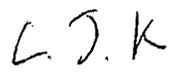
High Performance Liquid Chromatography

Instrument : Agilent 1200
Column : Inertsil ODS-2 (4.6 × 250 mm, 5 μm)
Mobile phase : A = 0.2% TFA Water
 B = Acetonitrile
Gradient : Time 0 20 50 50.1 60
 %B 20 60 60 20 20
Column Temperature : 40 °C
Flow rate : 1.0 mL/min
UV detection : 254 nm
Radiodetector : Lab Logic system, β-RAM 4
Radio detection : β-RAM
Integrator : Laura 4
Splitter : 0 % (off)
Flow Cell Volume : 500 μL
Scint flow : 3.0 mL/min
Cocktail : ULTIMA-FLO™ AP

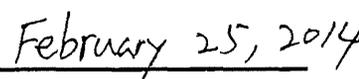
Caution: Not For Use In Humans Or Clinical Diagnosis. This product is intended for investigational or manufacturing use only. It is pharmaceutically unrefined and is not intended for use in humans. Responsibility for its use in humans, as a diagnostic reagent, and compliance with federal laws rests solely with the purchaser.



LAB Manager



QC Manager

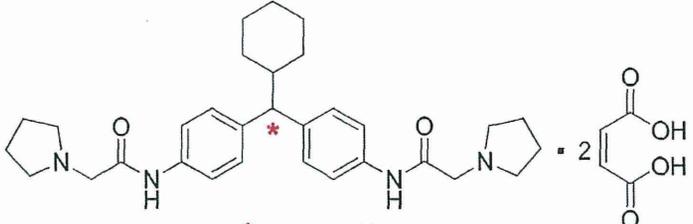


Date

Material Safety Data Sheet

1. IDENTIFICATION OF SUBSTANCE AND SUPPLIER	
Name on Label	[¹⁴ C]P092 maleate
Lot Number	K0262-16
Supplier	Curachem, Inc. Curachem, Inc. #837 Mecha-zone, 117, Hwanggeum-ro, Yangchon-eup, Gimpo-si, Gyeonggi-Do 415-843, Korea Phone: +82-31-999-7663; Fax: +82-31-999-7669 E-mail: yskim@curachem.com Emergency Telephone Number: +82-10-6717-7660
Alternative Names	None in common use.
2. COMPOSITION AND INFORMATION ON COMPONENTS	
Name	[¹⁴ C]P092 maleate
Radioisotope / Beta Energy	C-14 / 156keV
Total Activity	50 mCi (1850 MBq)
CAS No.	Not available
3. HAZARDS IDENTIFICATION	
Designation	Radioactive material
General Risk	May be toxic; avoid inhalation, contact with skin or eyes, and ingestion.
4. FIRST AID MEASURES	
Inhalation	Remove to fresh air. In cases of serious discomfort seek medical attention.
Eye Contact	Flush with copious amounts of water for at least 15 minutes. Seek urgent medical attention.
Skin Contact	Remove contaminated clothing. Rinse affected area with copious amounts of water. Rinse thoroughly. In case of skin damage seek urgent medical advice. Show the physician the container details.
Ingestion	Rinse out mouth and drink lots of water. Seek urgent medical attention and show physician the container details.
5. FIRE FIGHTING MEASURES	
Extinguishing Medium	Use fire fighting measures which suit the environment and take into account other materials which may be involved. In general, water-based extinguishers should not be used for fires involving organic materials. Use carbon dioxide or dry powder.
Protective Equipment	Wear self-contained breathing apparatus and protective clothing.
6. ACCIDENTAL RELEASE MEASURES	
Personal Protection	Avoid inhalation or contact of spilled material with skin or clothing. Wear protective equipment including chemical-resistant gloves, and eye protection. Keep unprotected persons away.
Environmental Protection	Take precautions to ensure product does not contaminate the ground or enter the drainage system.
Collection	Contain or adsorb, as appropriate. Minimize dust generation, where applicable. Dispose according to Section 13.
7. HANDLING AND STORAGE	
Handling	Chemicals should be used only by those trained in handling potentially hazardous materials. Chemical resistant gloves, eye protection and protective clothing should be worn. Operations should be carried out in an efficient fume hood or equivalent system. Avoid formation of dust.
Storage	Store in tightly sealed containers at -80 °C, unless indicated on bottle. Protect from moisture.
8. EXPOSURE CONTROLS AND PERSONAL PROTECTION	
Respiratory	Avoid inhalation of product. Handle in an efficient fume hood or equivalent system.
Eye	Avoid eye contact. Wear safety glasses, goggles or, for larger quantities, a full-face mask.
Hands and Body	Avoid skin contact. Wear chemical-resistant gloves and, for larger quantities, full arm and body protection. Wash hands thoroughly after handling.

Continued on next page

9. PHYSICAL AND CHEMICAL PROPERTIES	
Appearance	White Solid
Physical Constants	Radioactive material (100% β -decay : 156keV)
Molecular Formula	$^{14}\text{C}_{17}\text{H}_{38}\text{N}_4\text{O}_{10}$
Water Solubility	Not available
Flash Point	Not available
Formula Wt.	736.70
Density	Not available
Melting Point	Not available
Structure	 <p style="text-align: center;">* denotes ^{14}C label</p>
10. STABILITY AND REACTIVITY	
	No specific data regarding stability, incompatibility, or reactivity is currently available
11. TOXICOLOGICAL INFORMATION	
Toxicity Data	The toxicological properties of this compound have not been investigated. However, as a minimum precaution, it should be considered to be harmful. Precautions should be taken and procedures adopted to prevent exposure.
12. ECOLOGICAL EFFECTS	
General	Take care to prevent chemicals from entering the ground, water bodies, or drainage systems.
13. DISPOSAL CONSIDERATIONS	
Disposal	Disposal should be via an approved contractor according to all federal, state and local regulations.
14. TRANSPORT INFORMATION	
	UN2910
15. REGULATORY INFORMATION	
	Not Available
16. OTHER INFORMATION	
It must be recognized that the physical and chemical properties of any product may not be fully understood and that new, possibly hazardous products may arise from reactions between chemicals. The information given in this data sheet is based on our present knowledge and shall not constitute a guarantee for any specific product features and shall not establish a legally valid contractual relationship. THIS SUBSTANCE IS FOR RESEARCH AND DEVELOPMENT PURPOSES ONLY.	
Date of Last Revision	February 21, 2014

CURACHEM	QC Data of [¹⁴C]P092 maleate			
Chemical Purity	R-CODE	C0188	E-NOTE No.	K0262
	DATE	February 21, 2014		

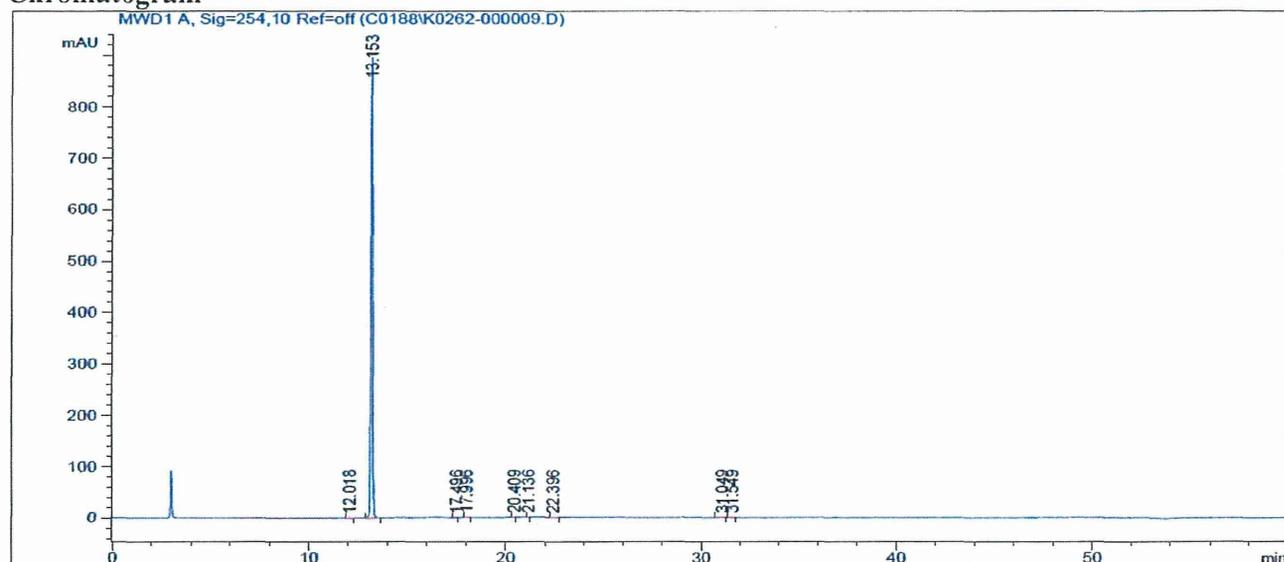
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Product Name	: P092 maleate	Lot Number	: -
Analysis Method	: C:\CHEM32\1\DATA\C0188\C0188.M	Data File	: C:\CHEM32\1\DATA\C0188\K0262-000009.D
Injection Date	: 02/21/2014 12:33:19 PM	Instrument	: Agilent 1200
Operator	: JungKu Lee	Comment	: -

HPLC Condition

Column	: Inertsil ODS-2 (4.6 × 250 mm, 5 μm)
Mobile phase	: A = 0.2% TFA Water B = Acetonitrile
Gradient	: Time 0 20 50 50.1 60 %B 20 60 60 20 20
Flow rate	: 1.0 mL/min
Column Temperature	: 40 °C
Concentration of sample	: 1.0 mg/mL (dissolved in 50% Acetonitrile)
Injection volume	: 5 μL
Detection	: UV 254 nm

Chromatogram



RetTime [min]	Area [mAU*s]	Height [mAU]	Area %
12.018	5.75557	0.886791	0.1050
13.153	5429.51758	897.82770	99.0947
17.496	2.23454	0.363457	0.0408
17.996	9.98884	1.39396	0.1823
20.409	2.12994	0.287053	0.0389
21.136	1.83861	0.286765	0.0336
22.396	4.54323	0.287542	0.0829
31.049	12.12930	0.783266	0.2214
31.549	10.98307	0.738117	0.2005

CURACHEM	QC Data of [¹⁴C]P092 maleate			
Chemical Purity	R-CODE	C0188	E-NOTE No.	K0262
	DATE	February 21, 2014		

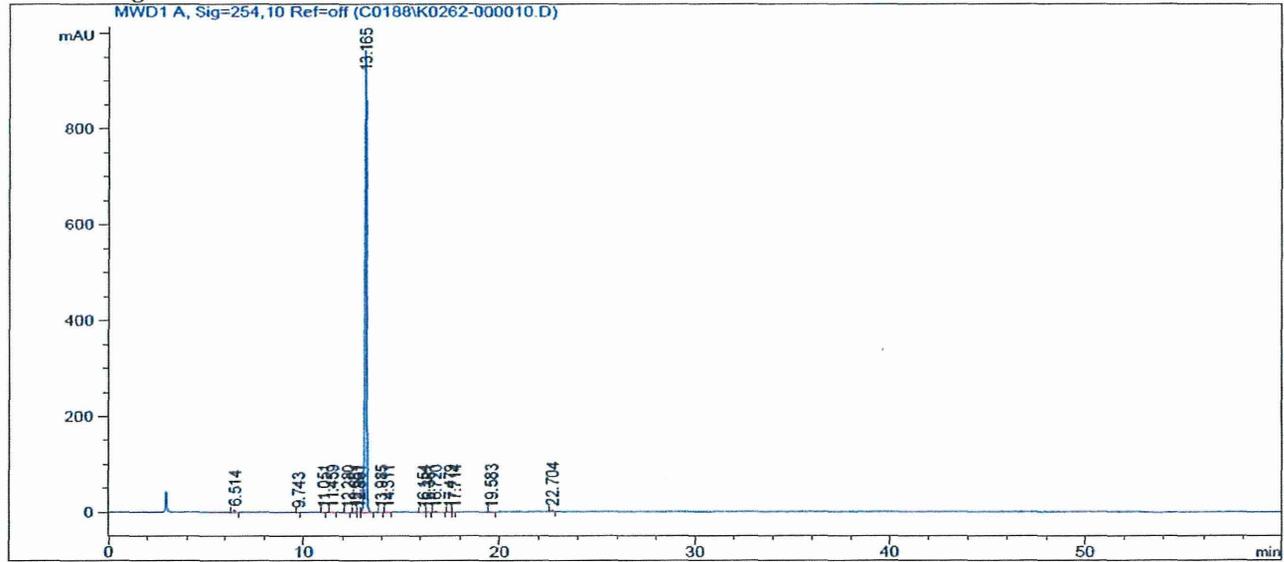
Information

Product Name	: [¹⁴ C]P092 maleate	Lot Number	: K0262-16
Analysis Method	: C:\CHEM32\1\DATA\C0188\C0188.M	Data File	: C:\CHEM32\1\DATA\C0188\K0262-000010.D
Injection Date	: 02/21/2014 01:35:09 PM	Instrument	: Agilent 1200
Operator	: JungKu Lee	Comment	: -

HPLC Condition

Column	: Inertsil ODS-2 (4.6 × 250 mm, 5 μm)
Mobile phase	: A = 0.2% TFA Water B = Acetonitrile
Gradient	: Time 0 20 50 50.1 60 %B 20 60 60 20 20
Flow rate	: 1.0 mL/min
Column Temperature	: 40 °C
Concentration of sample	: 1.0 mg/mL (dissolved in 50% Acetonitrile)
Injection volume	: 5 μL
Detection	: UV 254 nm

Chromatogram



RetTime [min]	Area [mAU*s]	Height [mAU]	Area %	RetTime [min]	Area [mAU*s]	Height [mAU]	Area %
6.514	31.93848	4.35561	0.5314	14.311	3.57558	0.387934	0.0595
9.743	0.720396	0.124885	0.0120	16.154	4.54859	0.550327	0.0757
11.051	1.36788	0.251780	0.0228	16.381	4.84589	0.801667	0.0806
11.459	4.29101	0.676973	0.0714	16.720	7.62009	0.441638	0.1268
12.280	3.60330	0.464964	0.0600	17.479	0.841130	0.106080	0.0140
12.651	7.81768	1.29458	0.1301	17.714	0.584975	0.0899495	0.009733
12.861	5.26462	0.855417	0.0876	19.583	5.10057	0.739182	0.0849
13.165	5899.35645	964.24988	98.1601	22.704	27.18540	3.80092	0.4523
13.985	1.27035	0.237603	0.0211				

CURACHEM	QC Data of [¹⁴C]P092 maleate		
Radiochemical Purity	R-CODE	C0188	E-NOTE No.
	DATE	February 21, 2014	

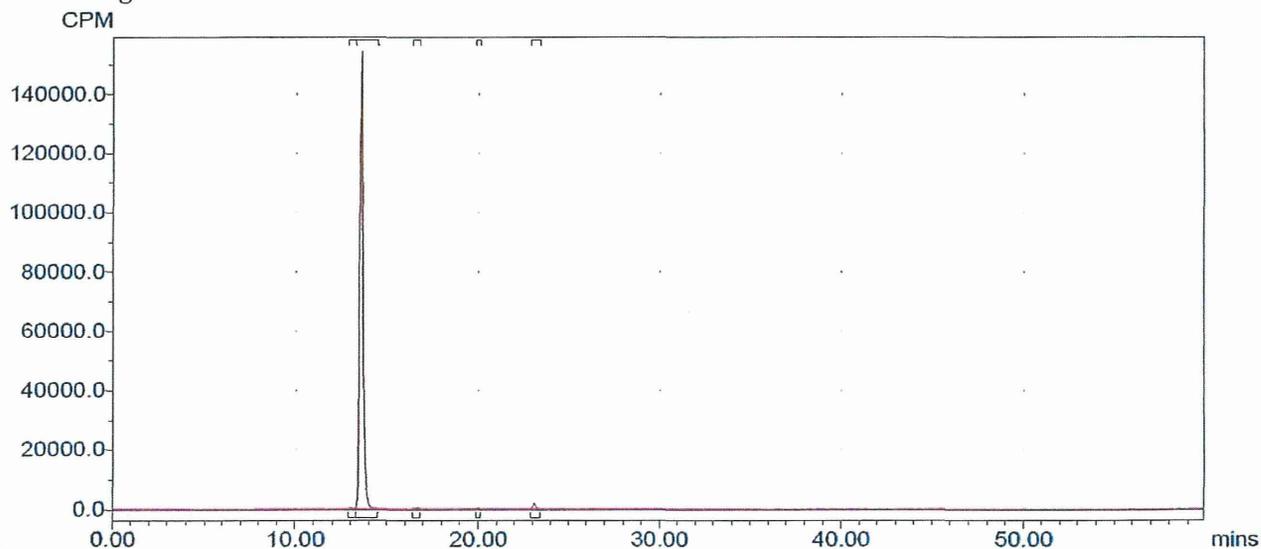
Information

Product Name	: [¹⁴ C]P092 maleate	Lot Number	: K0262-16
Analysis Method	: [¹⁴ C]P092 maleate	Data File	: C:\Laura\DATA\C0188-K0262 RUN 1
Injection Date	: 02/21/2014 01:35:09 PM	Instrument	: β-RAM Serial no 1107225
Channel	: ¹⁴ C	Dwell	: 6s
Cell Volume	: 500 μL	Cell Type	: Liquid
Efficiency	: 100.0%	Operator	: JungKu Lee

HPLC Condition

Column	: Inertsil ODS-2 (4.6 × 250 mm, 5 μm)
Mobile phase	: A = 0.2% TFA Water B = Acetonitrile
Gradient	: Time 0 20 50 50.1 60 %B 20 60 60 20 20
Flow rate	: 1.0 mL/min
Scint Flow rate	: 3.0 mL/min
Column Temperature	: 40 °C
Concentration of sample	: 1.0 mg/mL (dissolved in 50% Acetonitrile)
Injection volume	: 5 μL
Detector	: β-RAM

Chromatogram



Retention (mins)	Area (CPM)	%Total (%)	%ROI (%)
13.00	740.8	0.21	0.21
13.60	341230.4	98.50	98.54
16.60	684.8	0.20	0.20
20.00	358.4	0.10	0.10
23.10	3264.0	0.94	0.94
	346278.4	99.95	100.00
Total Area :		346436.8 CPM	