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KASHIMA LABORATORY LSI MEDIENCE CORPORATION STUDY DIRECTOR Masatomo Goto DATE January 26, 2015

Re-purification of [¹⁴C]P092 maleate

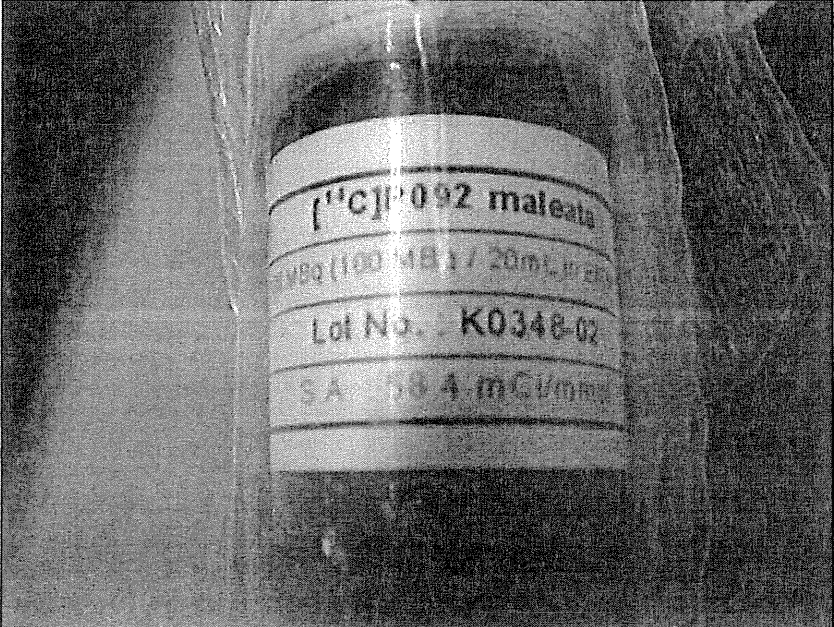
(Study No.:B141078)

LSI Medience Corporation

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Total 11 pages

Pictures: [¹⁴C]P092 maleate



Curachem, Inc. #837 Mecha-zone, 117, Hwanggeum-ro, Yangchon-eup, Gimpo-si, Gyeonggi-do 415-843,

Korea

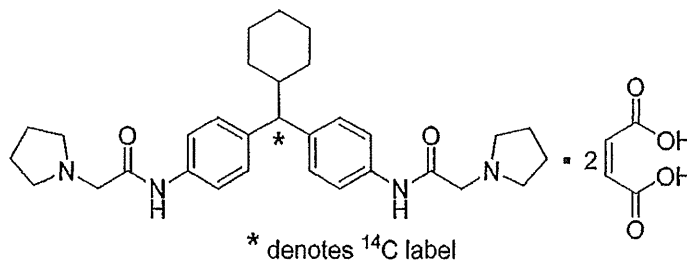
Phone : +82-31-999-7663 ; Fax : +82-31-999-7669

E-mail : yskim@curachem.com

CERTIFICATE OF ANALYSIS

(non-GMP, For Research Use Only)

Project No. C-0254



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	: K0348-02
DATE OF ANALYSIS	: December 26, 2014
SPECIFIC ACTIVITY	: 58.4 mCi/mmol by LSC
CHEMICAL PURITY	: 99.5% by UV-HPLC
RADIOCHEMICAL PURITY	: 98.9% by HPLC on-line 625TR & ProFSA3
PHYSICAL DESCRIPTION	: Ethanol solution
PACKAGING	: 450 MBq (12.2 mCi) in screw-capped amber 5 vials [100 MBq × 4 vials (conc: 100 MBq / 20 mL in EtOH), 50 MBq × 1 vial (conc: 50 MBq / 10 mL in EtOH)]
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

ESI Mass Spectroscopy

Instrument : Thermo LCQ-Fleet

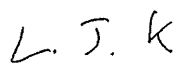
CHROMATOGRAPHIC DATA:

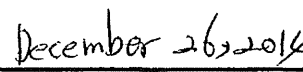
High Performance Liquid Chromatography

Instrument : Agilent 1100
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 : Perkinelmer, 625TR
Radio detection : FSA
Integrator : ProFSA3
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

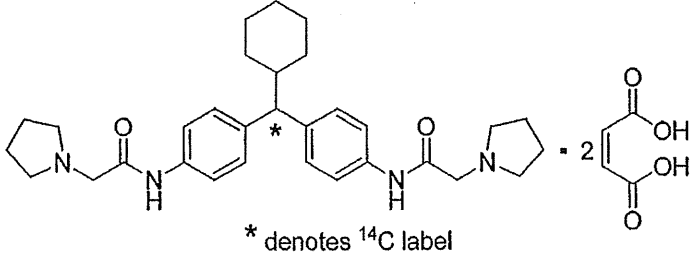

QC Manager


Date

Material Safety Data Sheet

1. IDENTIFICATION OF SUBSTANCE AND SUPPLIER	
Name on Label	[¹⁴ C]P092 maleate
Lot Number	K0348-02
Supplier	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	450 MBq (12.2 mCi)
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	Ethanol solution
Physical Constants	Not available
Molecular Formula	$^{14}\text{C}_{17}\text{H}_{28}\text{N}_4\text{O}_4$
Water Solubility	Not available
Flash Point	Not available
Formula Wt.	736.70
Density	Not available
Melting Point	Not available
Structure	 <p>* 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	December 26, 2014

CURACHEM	QC Data of [¹⁴C]P092 maleate			
Chemical Purity	R-CODE	C0254	E-NOTE No.	K0348
	DATE	December 26, 2014		

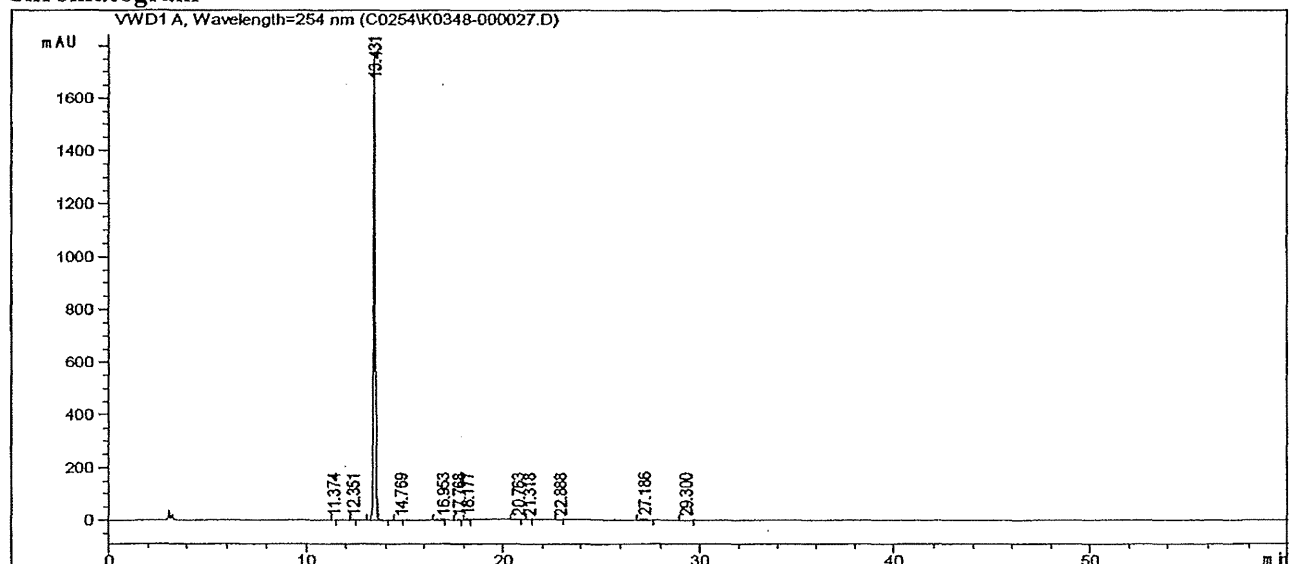
Information

Product Name	: P092 maleate	Lot Number	: -
Analysis Method	: C:\CHEM32\1\DATA\C0254\C0254_C.M	Data File	: C:\CHEM32\1\DATA\C0254\K0348-000027.D
Injection Date	: 12/26/2014 12:55:55 PM	Instrument	: Agilent 1100
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 Ethanol)
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 %
11.374	1.0543	0.1751	0.0087	18.177	18.9749	2.9878	0.1569
12.351	11.3013	1.9016	0.0934	20.763	5.4529	0.5858	0.0451
13.431	11989.6000	1752.8966	99.1334	21.318	3.7365	0.5760	0.0309
14.769	1.7464	0.1402	0.0144	22.888	1.8888	0.2029	0.0156
16.953	5.5134	0.4111	0.0456	27.186	42.7437	2.3285	0.3534
17.768	5.6644	0.7859	0.0468	29.300	6.7377	0.3283	0.0557

CURACHEM	QC Data of [¹⁴C]P092 maleate			
Chemical Purity	R-CODE	C0254	E-NOTE No.	K0348
	DATE	December 26, 2014		

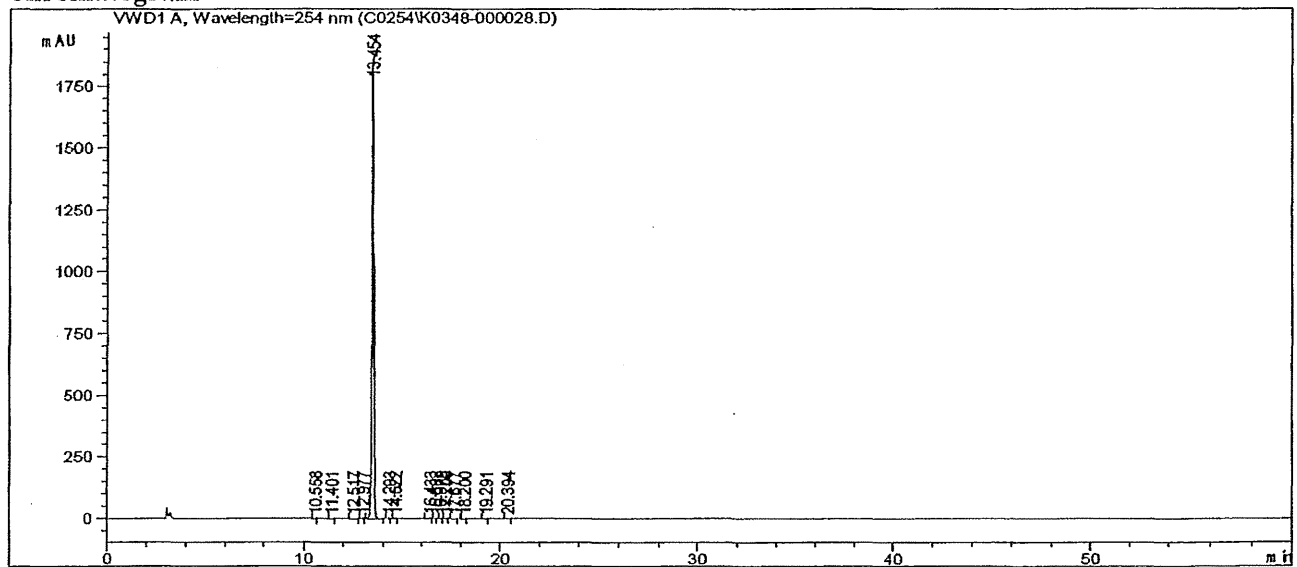
Information

Product Name	: [¹⁴ C]P092 maleate	Lot Number	: K0348-02
Analysis Method	: C:\CHEM32\1\DATA\C0254\C0254_C.M	Data File	: C:\CHEM32\1\DATA\C0254\K0348-000028.D
Injection Date	: 12/26/2014 01:59:49 PM	Instrument	: Agilent 1100
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 Ethanol)
Injection volume	: 5 μL
Detection	: UV 254 nm

Chromatogram



RetTime [min]	Area [mAU*s]	Height [mAU]	Area %
10.558	1.3526	0.2316	0.0103
11.401	6.5675	1.1129	0.0502
12.517	8.1471	0.4351	0.0623
12.977	11.6922	2.0838	0.0894
13.454	13014.2000	1871.9881	99.4651
14.293	8.3635	1.4474	0.0639
14.622	8.0892	0.9586	0.0618
16.433	7.8247	0.7074	0.0598

RetTime [min]	Area [mAU*s]	Height [mAU]	Area %
16.682	4.6019	0.7186	0.0352
16.979	1.6957	0.2489	0.0130
17.200	2.4896	0.2132	0.0190
17.677	4.2985	0.4451	0.0329
18.200	1.2323	0.1065	0.0094
19.291	1.0036	0.1038	0.0076
20.394	2.6255	0.3489	0.0201

CURACHEM	QC Data of [¹⁴C]P092 maleate			
Radiochemical Purity	R-CODE	C0254	E-NOTE No.	K0348
	DATE	December 26, 2014		

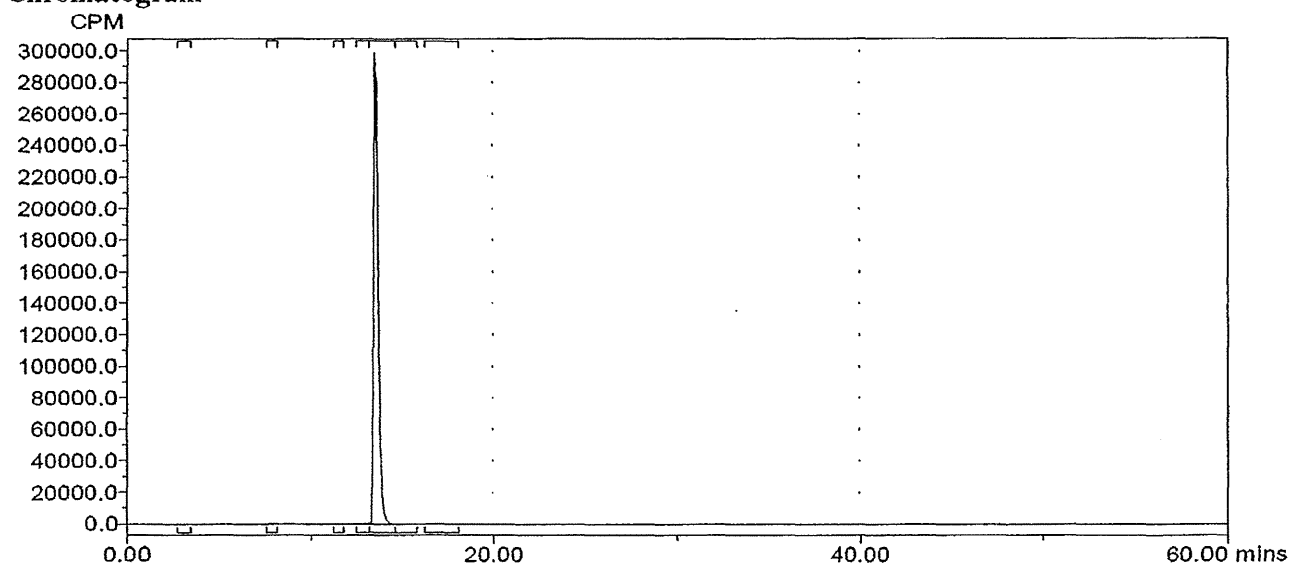
Information

Product Name	: [¹⁴ C]P092 maleate	Lot Number	: K0348-02
Analysis Method	: C0254-K0348.M	Data File	: C:\ProFSA\DATA\C0254-K0348\20141226-01
Injection Date	: 12/26/2014 01:59:49 PM	Instrument	: 625TR Serial No. 432630
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
Eluate 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 Ethanol)
Injection volume	: 5 µL
Detector	: FSA

Chromatogram

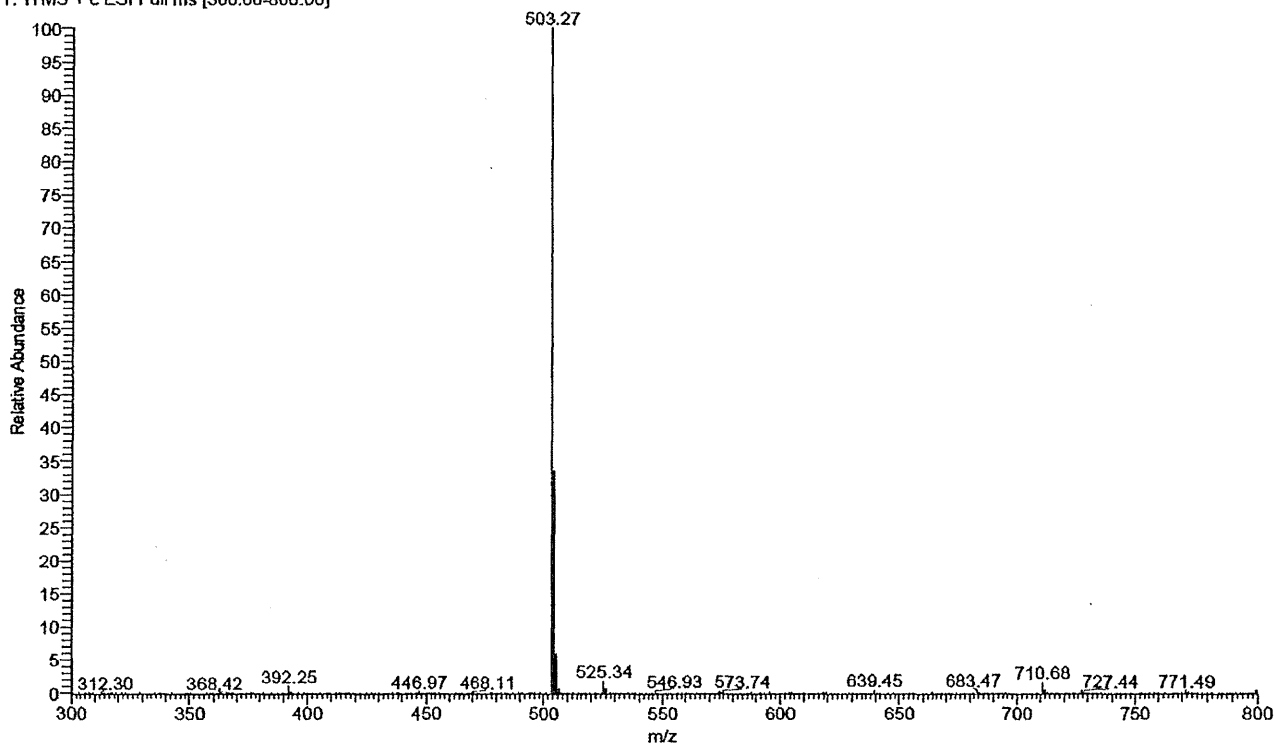


Retention (mins)	Area (CPM)	%Total (%)	%ROI (%)
2.90	1051.0	0.12	0.12
7.90	1254.0	0.15	0.15
11.40	713.0	0.08	0.08
13.10	1619.0	0.19	0.19

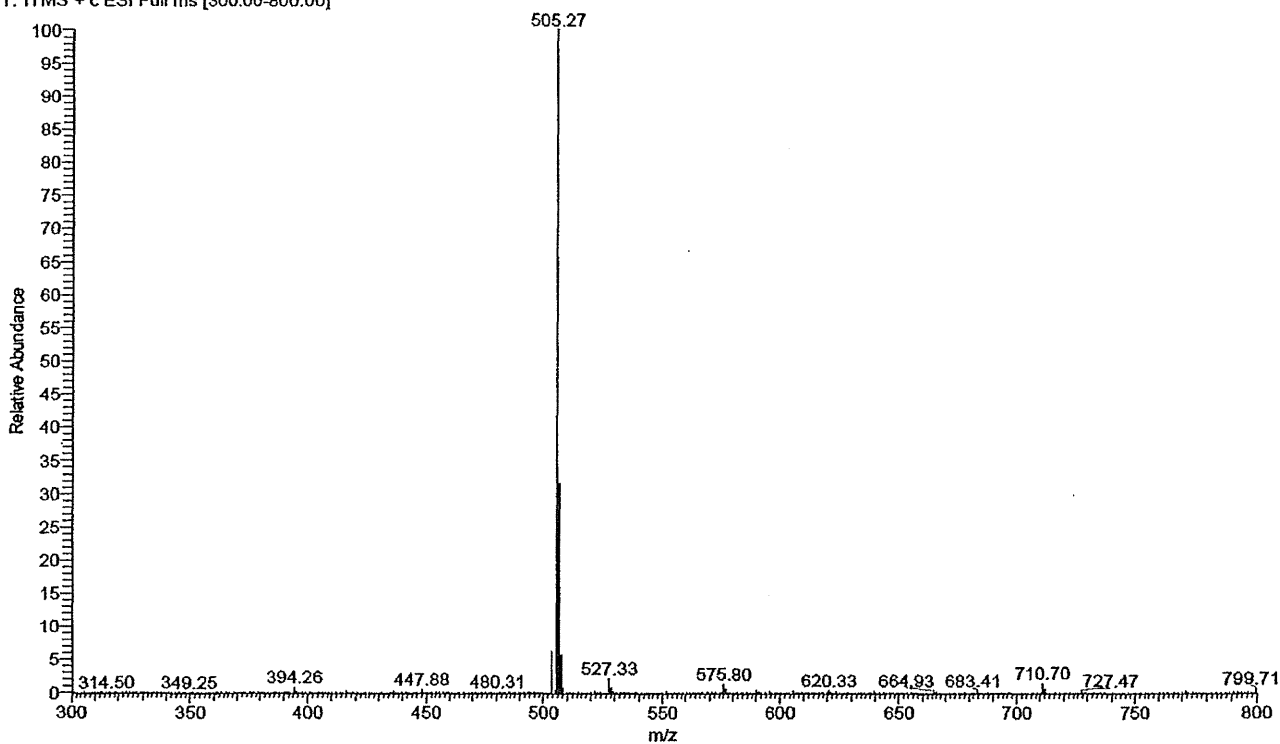
Retention (mins)	Area (CPM)	%Total (%)	%ROI (%)
13.50	844670.0	98.88	98.88
15.50	2252.0	0.26	0.26
16.50	2663.0	0.31	0.31
854222.0		100.00	100.00
Total Area :		854168.0 CPM	

CURACHEM		QC Data of [¹⁴ C]P092 maleate		
MS	R-CODE	C0254	E-NOTE No.	K0348
	DATE	December 26, 2014		

P092 maleate NL: 9.22E4
T: ITMS + c ESI Full ms [300.00-800.00]



[¹⁴C]P092 maleate NL: 9.85E4
T: ITMS + c ESI Full ms [300.00-800.00]



6. P092 マレイン酸塩の投与液濃度 確認のための分析法バリデーション

本写しは原本と相違ありません

最終報告書

B141088

株式会社 L S I メディエンス 鹿島研究所

Analytical Method Validation

2015年1月13日

2015年1月13日

試験責任者 紺野 邦裕 印

株式会社 L S I メディエンス
鹿島研究所

試験責任者：

紺野 邦裕

紺野 邦裕

分析担当者： 湊 健一

表 題： P092 マレイン酸塩の投与液濃度確認のための分析法バリデーション
試験番号： B141088
被験物質： P092 マレイン酸塩
ロット番号： FA5QJ-QG
試験委託者： 国立大学法人岐阜大学
分析法： HPLC 法
実施日： 2014年12月22～24日
目的： 投与液（媒体：生理食塩液）中 P092 濃度を測定するための分析法の妥当性を検証した。
試験結果： 特異性確認のクロマトグラム上、P092 フリー体の溶出位置に妨害ピークは認められず、直線性、再現性及び回収率は許容基準を満たした。従って、HPLC 法を用いた本分析法は十分に信頼できると判断した。

I. 濃度測定法のバリデーション結果

項目	許容基準	結果
特異性	妨害ピークが確認された場合、ST-2 の P092 フリー体ピーク面積の 5%以下であること。	妨害ピークは認められなかった。(Figure 1)
直線性	相関係数 (r) ≥ 0.995	$r = 0.9999$
再現性	C.V. $\leq 5\%$	0.9% (0.5 $\mu\text{g/mL}$, n=3) 0.4% (1 $\mu\text{g/mL}$, n=3) 0.4% (2 $\mu\text{g/mL}$, n=3)
回収率	対理論値：100 \pm 10%以内	98.2% (0.001 mg/mL, n=3) 98.7% (50 mg/mL, n=3)

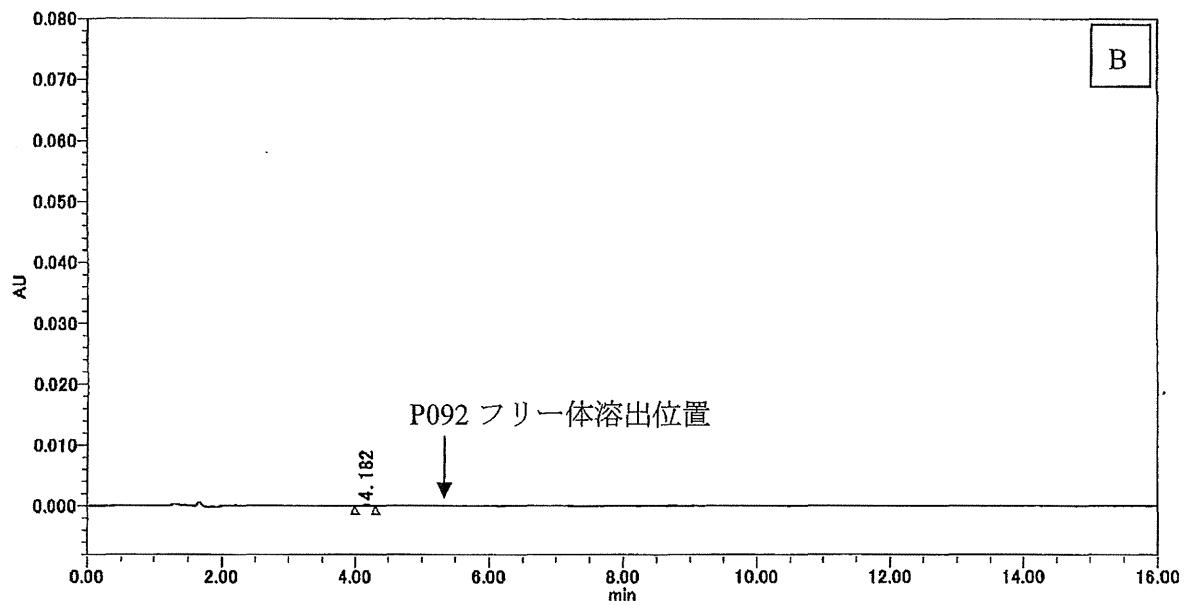
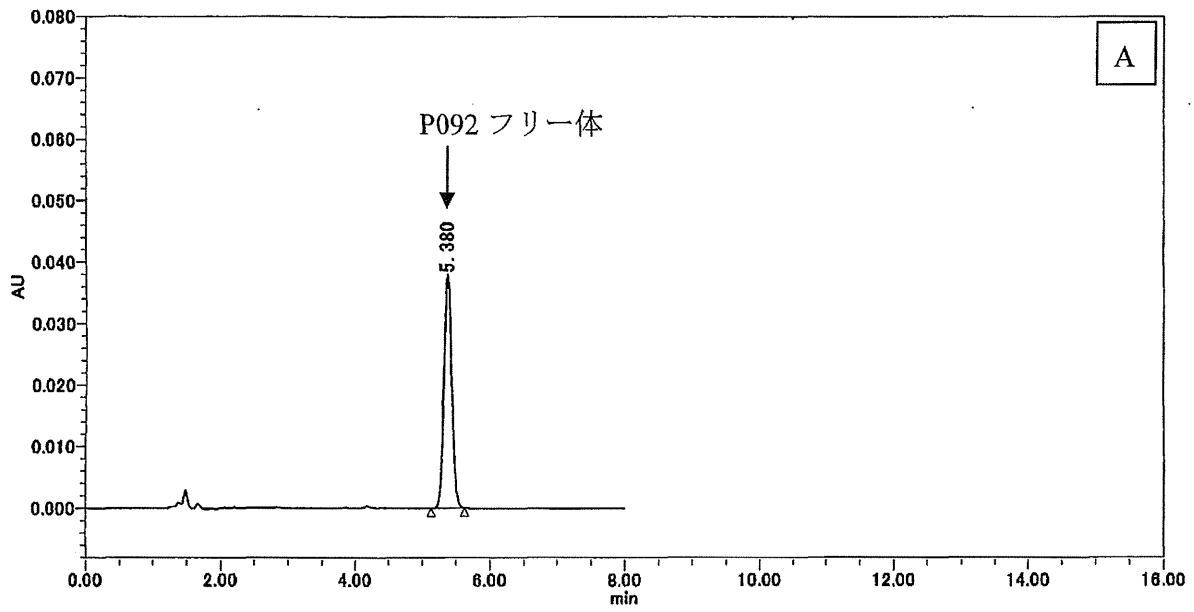


Figure 1 クロマトグラム例
A : ST-2 (1 µg/mL), B : SF


7. Bioanalytical Method Validation
for Determination of P092
in Rat and Monkey Blood

最終報告書

Bioanalytical Method Validation for Determination of P092 in Rat and Monkey Blood

(試験番号 : B141089)

株式会社LSIメディエンス

本写しは原本と相違ありません
(株)LSIメディエンス 鹿島研究所
2015年3月19日
試験責任者 西田 紀子 

1. 陳述書

表 題： Bioanalytical Method Validation for Determination of P092 in Rat and Monkey Blood

試験番号： B141089

本試験は以下の基準に従って実施され、本報告書はその結果を正しく記載したものである。

(申請資料の信頼性の基準)

医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律施行規則 第43条

試験責任者：

2013年3月19日 西田 紀子

西田 紀子

株式会社LSIメディエンス

創薬支援事業本部 試験研究センター

分析代謝研究部 薬物分析グループ

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