Australian Government

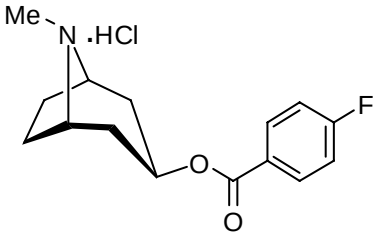
National Measurement Institute

REFERENCE MATERIAL ANALYSIS REPORT

Report ID: D949.2013.01

Compound Name: **4-Fluorotropacocaine hydrochloride**
Collection Number: D949
Chemical Formula: $C_{15}H_{18}FNO_2.HCl$
CAS Number: N/A (HCl), 172883-97-5 (base)
Structure:

Description: Off-white powder
Batch Number: 09-D-30
Molecular Weight: 299.8 (HCl), 263.3 (base)
Release date: 26th April 2010



Synonyms: *p*-Fluorotropacocaine hydrochloride
exo-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 4-fluorobenzoic acid ester hydrochloride

Purity (mass fraction): 81.6 ± 5.0 % (95% coverage interval)

Purity estimate obtained from a combination of traditional analytical techniques. Purity estimate obtained by subtraction from 100% of total impurities by GC-FID, Karl Fischer analysis, thermo gravimetric analysis and ^{1}H NMR analysis. Supporting evidence is provided by quantitative NMR analysis against a certified internal standard of potassium hydrogen maleate.

The material contains high level non-volatile residues assessed by thermal gravimetric analysis. The non-volatiles were not identified. The material has shown a tendency to absorb moisture. Although this material has demonstrated stability in its organic purity, it should be considered for use as an internal standard only.

GC-FID	Instrument:	Agilent 6890N	
	Column:	HP-1, 29.9 m x 0.32 mm I.D. x 0.25 µm	
	Program	100 °C (1 min), 15 °C/min to 200 °C (3 min), 20 °C/min to 300 °C (3 min) [2010]	
	Program	120 °C (1 min), 8 °C/min to 200 °C (3 min), 30 °C/min to 300 °C (3 min) [2011]	
.	Injector:	250 °C	Detector Temp: 320 °C
	Carrier:	Helium	Split ratio: 20/1
	Relative peak area response of main component:		
	Initial analysis:	Mean = 99.0%, s = 0.02% (7 sub samples in duplicate, February 2010)	
	Re-analysis:	Mean = 99.1%, s = 0.02% (5 sub samples in duplicate, January 2012)	
	Re-analysis:	Mean = 99.2%, s = 0.04% (5 sub samples in duplicate, December 2012)	
GC-FID:	Instrument:	Varian CP-3800	
	Column:	VF-1MS, 29.82 m × 0.32 mm I.D. × 0.25 µm	
	Program	100 °C (1 min), 15 °C/min to 200 °C (3 min), 20 °C/min to 300 °C (3 min)	
	Injector:	250 °C	Detector Temp: 320 °C
	Carrier:	Helium	Split ratio: 20/1
	Relative peak area response of main component:		
	Initial analysis:	Mean = 99.1%, s = 0.04% (7 sub samples in duplicate, January 2010)	
GC-FID:	Instrument:	Varian CP-3800	
	Column:	VF-1MS, 29.8 m × 0.32 mm I.D. × 0.25 µm	
	Program	100 °C (1 min), 15 °C/min to 200 °C (3 min), 20 °C/min to 300 °C (3 min)	
	Injector:	250 °C	Detector Temp: 320 °C
	Carrier:	Helium	Split ratio: 20/1
	Relative peak area response of main component:		
	Initial analysis:	Mean = 99.2%, s = 0.01% (7 sub samples in duplicate, January 2010)	

QNMR:	Instrument:	Bruker Avance III-400
	Field strength:	400 MHz Solvent: D_2O
	Internal standard:	Potassium hydrogen maleate
	Purity estimate:	Mean = 89.8%, s = 1.3 (5 sub samples, February 2010).
Thermogravimetric analysis:		Volatile residue < 1.0 %, non volatile residue 8.0 % mass fraction (March 2010) Volatile residue 7.3 %, non volatile residue 6.6 % mass fraction (January 2011)
Karl Fischer analysis:		Moisture content 1.2 % mass fraction (February 2010) Moisture content 7.1 % mass fraction (January 2011) Moisture content 10.3 % mass fraction (January 2012) Moisture content 9.7 % mass fraction (December 2012)

Spectroscopic and other characterisation data

GC-MS:	Instrument:	Agilent 6890/5973
	Column:	VF-1MS, 14.9 m × 0.25 mm I.D. × 0.25 μm
	Program:	120 °C (10min), 15 °C/min to 300 °C (3 min)
	Injector:	250°C Transfer line temp: 300 °C
	Carrier:	Helium, 1.0 mL/min Split ratio: 20/1
	The retention time of the parent compound is reported along with the major peaks in the mass spectrum. The latter are reported as mass/charge ratios and (in brackets) as a percentage relative to the base peak	
	14.7 min: 263 (M^+, 25), 140 (9), 124 (100), 94 (37), 82 (66), 67 (15), 42 (13) m/z	
TLC:	Conditions:	Kieselgel 60F_{254} Methanol/$CHCl_3$ (20:80) Single spot observed, R_f = 0.30 Visualization with UV light (254 nm)
IR:	Instrument:	BioRad FTS3000MX FT-IR
	Range:	4000-500 cm^{-1}, KBr powder
	Peaks:	2962, 2824, 2678, 2490, 1718, 1603, 1508, 1292, 1116, 861, 770, 604 cm^{-1}
^{1}H NMR:	Instrument:	Bruker Avance III-400
	Field strength:	400 MHz Solvent: CD_3OD (3.31 ppm)
	Spectral data:	δ 2.14-2.22 (4H, m), 2.39-2.44 (4H, m), 2.85 (3H, s), 4.02-4.04 (2H, m, *J* = 3.5 Hz), 5.40 (1H, dddd, *J* = 6.1, 6.1, 11.0, 11.0 Hz), 7.19-7.24 (2H, m), 8.05-8.09 (2H, m) Isopropanol was observed in the ^{1}H NMR spectrum at 0.10 % mass fraction Coupling between fluorine and hydrogen was observed.
^{13}C NMR:	Instrument:	Bruker Avance III-500
	Field strength:	125 MHz Solvent: CD_3OD (49.0 ppm)
	Spectral data:	δ 25.3, 36.2, 38.9, 64.6, 65.9, 116.7 (d, *J* = 22.5 Hz), 127.4 (d, *J* = 3.2 Hz), 133.4 (d, *J* = 9.5 Hz), 166.1, 167.4 (d, *J* = 253 Hz) ppm Coupling between fluorine and carbon was observed.
Melting point:		270 °C (dec.)
Microanalysis:		Found: C = 54.0 %; H = 5.9 %; N = 4.1 % (February 2010) Calc: C = 60.1 %; H = 6.4 %; N = 4.7 % (Calc. for $C_{15}H_{18}FNO_2.HCl$)

Expiration of certification
The property values are valid till 6th December 2017, i.e. three years from the date of re-certification provided the **unopened** material is handled and stored in accordance with the recommendations below. The material as issued in the unopened container and stored as recommended below should be suitable for use beyond this date, subject to confirmation of batch stability from the issuing body.

The expiry date/shelf life does not apply to sample bottles that have been opened. In such cases it is recommended that the end-user conduct their own in-house stability trials.

The long-term stability of the compound in solution has not been examined.

This material has been given a shelf life of 3 years from the date of re-certification. The material will be re-tested on an annual basis to ensure that the property values are still valid. In the event a product fails the stability trial, notification will be sent to all impacted customers.

In the absence of stability data the measurement uncertainty at the 95% coverage interval has been expanded to accommodate any potential change in the property value. The stability component has been estimated from stability trials conducted on similar materials by NMI Australia over the last 10 years.

Homogeneity assessment
The homogeneity of the material was assessed using purity assay by GC with flame ionisation detector on five randomly selected 1-2 mg samples of the material. The material was judged to be homogeneous at this level of sampling as the variation in analysis results between samples was not significantly different at a 95% confidence level from that observed on repeat analysis of the same sample.

Recommended storage
When not in use this material should be stored at or below 20 ºC in a closed container in a dry, dark area.

Intended Use
For ***in vitro*** laboratory analysis only.

Caution
Treat as hazardous substance. Use appropriate work practices when handling to avoid skin or eye contact, ingestion or inhalation of dust.

Legal notice
Neither NMI nor any person acting on NMI's behalf assumes any liability with respect to the use of, or for damages resulting from the use of, this reference material or the information contained in this certificate.

Authorised by:

S. R. Davies

Dr Stephen R. Davies,
Team Leader,
Chemical Reference Materials, NMI.
Dated: 1 January, 2013.

Characterisation data and property values specified in this report supersede those in all reports issued prior to 24th December 2012.