
HPLC METHODS FOR RECENTLY APPROVED PHARMACEUTICALS

George Lunn



**WILEY-
INTERSCIENCE**

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PREFACE

This book is a collection of procedures for the analysis of more than 390 pharmaceuticals using high-performance liquid chromatography (HPLC) and covers the literature up to the end of 2003. The current volume is a continuation of *HPLC Methods for Pharmaceutical Analysis*, published in four volumes from 1997 to 2000. The previous volumes described methods published in the literature through the middle of 1998.

The current work lists procedures for the analysis of drugs in three broad categories:

- Drugs that have been approved since the previous volumes were published.
- Drugs that were approved when the previous volumes were published but for which analytical methods were not then available in the literature.
- Drugs for which procedures allowing determination in a blood matrix have only become available since the previous volumes were published.

Please note that mention of a drug does not necessarily mean that it is currently approved for use in the United States or indeed in any country.

Despite the ready availability of computer-aided literature, searching this resource is not exploited as much as it might be. One reason for this reluctance is, of course, that a computer search merely produces a listing of possibly relevant references. Tedious and time-consuming searches in the library are necessary to find the most relevant reference that can be turned into a practical analytical procedure in the searcher's own laboratory. The reference finally chosen will, naturally, depend on the individual circumstances, such as the matrix in which the drug is present, availability of equipment, and so on. This book circumvents this lengthy process by providing a number of abstracted and evaluated procedures for the analysis of each drug. The analyst can rapidly identify a relevant procedure and put it into practice.

In addition to the analytical matrix, other factors may be important when choosing an analytical procedure. Accordingly, we have noted such features of the analytical procedures as sensitivity, mode of detection, other compounds that interfere with the analysis, other drugs that may be determined at the same time, and so on.

Readers familiar with our previous publications, *HPLC Methods for Pharmaceutical Analysis, Volumes 1–4* (George Lunn and Norman R. Schmuff, John Wiley, New York, 1997–2000) and *Handbook of Derivatization Reactions for HPLC* (George Lunn and Louise C. Hellwig, John Wiley, New York, 1998), will notice many similarities. The abstract structure is very similar, and the philosophy that the procedures

should be reproducible without reference to the original literature is unchanged. A new feature is that the retention times (in minutes) of other drugs that may be determined using the same system have been added in parentheses after the drug name. Other data, such as the limit of detection (LOD), may also be added. The retention time is the number without units. Unlike the previous volumes, this book is not available on a CD in an electronic form.

At the end of the book a Cumulative Index and a Cross-Index to Other Substances are provided. The Cumulative Index provides a comprehensive listing of the drugs covered in this book and the previous volumes. The Cross-Index lists the other compounds that may also be chromatographed under the conditions described in the monographs in this book. Using the information in the monographs it may be possible to develop chromatographic procedures for these compounds.

GEORGE LUNN

ACKNOWLEDGEMENTS

I am grateful for the use of the National Institutes of Health Library, the FDA Medical Library, and the National Library of Medicine and I would like to express my appreciation for the hard work of the staff of these libraries, particularly those diligent workers who reshelve the journal volumes after one of my forays. Although many people have helped with the preparation of this work the mistakes are my own. I would appreciate hearing from anyone who has corrections, comments, or suggestions. I can be reached at lunng@cdcr.fda.gov.

The content of this volume does not necessarily reflect the views or policies of the Food and Drug Administration, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. Also, mention of a drug does not necessarily mean that it is currently approved for use in the United States or indeed in any country.

G.L.

ABOUT THIS BOOK

SCOPE

Newly approved drugs were identified from a variety of sources including the FDA's annual lists of drug approvals (available at www.fda.gov/cder) and *Annual Reports in Medicinal Chemistry* published by Elsevier/Academic Press.

The journals routinely surveyed for relevant articles are:

American Journal of Health-System Pharmacy

Analyst

Analytica Chimica Acta

Analytical Chemistry

Analytical Letters

Analytical Sciences

Antimicrobial Agents and Chemotherapy

Arzneimittelforschung

Biological and Pharmaceutical Bulletin

Biomedical Chromatography

Biopharmaceutics and Drug Disposition

Chemical and Pharmaceutical Bulletin

Chromatographia

Clinical Chemistry

Clinical Pharmacology and Therapeutics

Drug Metabolism and Disposition

Farmaco

Food Additives and Contaminants

Journal of Analytical Toxicology

Journal of AOAC International

Journal of Chromatographic Science

Journal of Chromatography, Part A and Part B

Journal of Clinical Pharmacology

Journal of Forensic Sciences

Journal of Liquid Chromatography & Related Technology
Journal of Pharmaceutical and Biomedical Analysis
Journal of Pharmaceutical Sciences
Journal of Pharmacology and Experimental Therapeutics
Pharmaceutical Research
Pharmazie
Therapeutic Drug Monitoring
Xenobiotica

Other journals were consulted when relevant articles were identified by computer searches.

The literature was surveyed from 1998 through the end of 2003, although methods from some older articles (and a few from 2004) are included.

NOMENCLATURE

Each chapter is headed by the name and structure of the target compound as well as other useful data such as the CAS Registry Number, molecular formula, molecular weight, and Merck Index number (from the 13th edition).¹ More useful information such as melting point, solubility, optical rotation, references to reviews, and so on can be found in the Merck Index.

In general, the United States Adopted Name (USAN)² is used throughout to identify each drug. Names of derivatives, such as esters, which would have different chromatographic properties, are identified by placing the derivative name in parentheses after the retention time.

Increasingly, drugs previously marketed as racemates are being marketed as a single enantiomer with the name changed to reflect the enantiomer. For example, levofloxacin is the levorotatory form of ofloxacin. For an achiral HPLC method, the chromatography of a single enantiomer is no different from that of the racemate. In general, in this work and the preceding works, we have listed HPLC procedures under the name of the racemate rather than the single enantiomer. The interested reader is referred to the USP Dictionary² (page 1208) for the naming conventions used. Generally:

Levo rotatory	S isomer	Prefix lev/levo-
Levo rotatory	R isomer	Prefix ar-
Dextro rotatory	R isomer	Prefix dex/dextro-
Dextro rotatory	S isomer	Prefix es-

For racemates, the rac- prefix is used.

In some cases, the chiral prefix is used. Thus, the following list shows the prefixes that are used in the different volumes:

Dexrazoxane in this volume
 Dextromethorphan in Volume 2
 Dextromoramide in Volume 2
 Dextrothyroxine in Volume 2

Levallorphan in Volume 3
 Levamisole in Volume 3
 Levobunolol in Volume 3
 Levodopa in Volume 3
 Levonordefrin in Volume 3 and this volume
 Levorphanol in Volume 3
 Levosimendan in this volume
 Levothyroxine in Volumes 1 and 3.

More generally, the name of the racemic compound is used. Thus,

For	Consult	Volume
Arformoterol	Formoterol	3, this volume
Dexamisole	Levamisole	3
Dexamphetamine	Amphetamine	2
Dexbrompheniramine	Brompheniramine	2
Dexbudesonide	Budesonide	2
Dexchlorpheniramine	Chlorpheniramine	2
Dexfenfluramine	Fenfluramine	3
Dexibuprofen	Ibuprofen	1, 4
Dexketoprofen	Ketoprofen	1, 4
Dexmedetomidine	Medetomidine	This volume
Dexmethylphenidate	Methylphenidate	1
Dexpropranolol	Propranolol	4
Dexsotalol	Sotalol	4
Dextroamphetamine	Amphetamine	2
Dextropropoxyphene	Propoxyphene	1, 4
Dexverapamil	Verapamil	1, 4
Esatenolol	Atenolol	1, 2
Escitalopram	Citalopram	2
Esflurbiprofen	Flurbiprofen	3
Esketamine	Ketamine	3
Esomeprazole	Omeprazole	1, 3
Esoxybutynin chloride	Oxybutynin chloride	3
Eszopiclone	Zopiclone	4
Levalbuterol	Albuterol	1, 2
Levamphetamine	Amphetamine	2
Levamphetamine	Amphetamine	2
Levcycloserine	Cycloserine	2
Levdobutamine	Dobutamine	2
Levmetamfetamine	Methamphetamine	3
Levobetaxolol	Betaxolol	2
Levobupivacaine	Bupivacaine	2
Levocarnitine	Carnitine	2
Levocetirizine	Cetirizine	2
Levodropropizine	Dropropizine	2, this volume

Levofenfluramine	Fenfluramine	3
Levofloxacin	Ofloxacin	1, 3
Levofuraltadone	Furaltadone	3
Levoleucovorin	Leucovorin	3
Levomenthol	Menthol	3, this volume
Levomethadone	Methadone	3
Levomoprolol	Moprolol	3
Levonorgestrel	Norgestrel	1
Levopropoxyphene	Propoxyphene	1, 4
Levopropylhexedrine	Propylhexedrine	4, this volume
Levosalbutamol	Albuterol	1, 2
Levosulpiride	Sulpiride	4
Racementhol	Menthol	3, this volume
Racemethorphan	Dextromethorphan	2
Racemetirosine	Metyrosine	This volume
Racemorphan	Levorphanol	3
Racephedrine	Ephedrine	3
Racepinephrine	Epinephrine	3

BIBLIOGRAPHIES

For reasons of space, it is not possible to abstract every relevant paper, and so at the end of some chapters an Annotated Bibliography lists other relevant papers. After the citation, a few features of the method that are not obvious from the title of the paper may be briefly mentioned to help the reader decide if this paper may be of use. For example, the limit of quantitation of the method may be cited. Unless otherwise mentioned, it may be assumed that a method involves liquid–liquid extraction of a biological fluid from a human and uses reversed-phase HPLC with UV detection. Thus, if a method uses solid-phase extraction (SPE) or fluorescence detection, this will be mentioned.

ABSTRACT STRUCTURE

The detailed procedures given normally contain the following sections. Of course, not all papers give full details, so some sections may be missing.

- Matrix
- Sample preparation
- Guard column
- Column
- Mobile phase
- Flow rate
- Injection volume
- Retention time
- Detector

Internal standard
 Column temperature
 Extracted
 Simultaneous
 Also
 Noninterfering
 Interfering
 Limit of detection
 Limit of quantitation
 Key words
 Reference

ABSTRACT CONVENTIONS

Also	Compounds that can be analyzed at the same time. It is not specified whether they interfere, but they can be extracted. See also Extracted, Simultaneous.
Column	Dimensions are length (mm) \times internal diameter (mm), and the material is stainless steel unless otherwise indicated.
Column temperature	If other than ambient (all temperatures are in degrees C).
Derivatization	Pre-column unless otherwise mentioned (in Key Words).
Detector	Wavelengths in nanometers
Extracted	Compounds that can be extracted from the matrix in question and analyzed at the same time and do not interfere. See also Also, Simultaneous.
Flow rates	In milliliters per minute.
Guard column	Dimensions are length (mm) \times internal diameter (mm).
Injection volume	In microliters (μL). Injection volume may be either the volume actually injected or the volume of the injection loop. If it is the volume actually injected, this value is also given in the Sample preparation section. If the actual injection volume is not given in the Sample preparation section, the Injection volume given is that of the injection loop.
Interfering	Compounds that interfere with the analysis of the target compound. Compounds that interfere with the chromatography of the internal standard (IS) are listed under simultaneous (another IS can always be selected or an external standard procedure can be used).
Matrix	A controlled vocabulary is used (see below)
Mobile phase	Ratios are v/v and gradients are linear, unless otherwise noted. Times given when describing gradient elution and other procedures such as column switching are the times for each step, e.g., "MeOH:water 15:85 for 4 min, to 50:50 over 2 min, maintain at 50:50 for 4 min." If we were to include the cumulative times (t) in the example above it would read: "MeOH:water 15:85 for 4 min ($t = 4$), to 50:50 over 2 min ($t = 6$), maintain at 50:50 for 4 min ($t = 10$)."

Noninterfering	Compounds that do not interfere with the analysis for various reasons, e.g., they are not extracted, they are not detected.
Retention time	In minutes. This is frequently estimated from a reproduced chromatogram, and so the accuracy may not be great. When available, retention times are given for the analyte, the internal standard, and other compounds that may be chromatographed under the same conditions. For the internal standard and other compounds that may be chromatographed under the same conditions, the retention times are given in parentheses after the compound name.
Simultaneous	Compounds that can be analyzed at the same time and do not interfere. Note that the compound cannot necessarily be extracted from the matrix in question (although it may be). See also Also, Extracted.
SPE	For the sake of consistency, conditioning procedures for solid-phase extraction (SPE) cartridges are always described at the beginning of the sample preparation sections. Bear in mind, however, that the conditioning procedure should be carried out just prior to use. Thus, if sample preparation is a lengthy procedure, it may be necessary to delay SPE cartridge conditioning until the step requiring the cartridge.
Species	If other than human, noun is used instead of adjective, e.g., cow not bovine. In some cases, human may be specified. For example, if <i>both</i> human blood and rat blood are analyzed, <i>both</i> human and rat will be indicated (in Key Words).

MATRIX

To help with searching, a controlled vocabulary is used to limit the number of terms in the matrix section. For example, the terms raw material, drug substance, or API (active pharmaceutical ingredient) are not used; the term bulk is used instead. In a number of cases, the matrix is associated with various key words, which can be used to narrow the search. For example, the matrix term blood has the key words plasma, serum, and whole blood associated with it. Thus, if you are interested in the determination of the drug in blood in general, you should look in the matrix field for blood. If, however, you are specifically interested in finding the drug in plasma, you should look in the key words field for plasma.

Matrix	Associated Key Words
Bile	
Blood	Plasma, serum, whole blood
Bulk	
CSF	
Formulations	Capsules, creams, injections, ointment, tablets, etc.
Microsomal incubations	

Milk	
Perfusate	
Reaction mixtures	
Saliva	
Tissue	Brain, heart, kidney, liver, muscle, spleen, etc.
Urine	

ABBREVIATIONS

BHT	2,6-Di-tert-butyl-4-methylphenol, butylated hydroxytoluene
DMSO	Dimethyl sulfoxide
E	Electrochemical detection
em	Emission wavelength
EtOH	Ethanol
ex	Excitation wavelength
F	Fluorescence detection
GPC	Gel permeation chromatography
h	Hour
HPLC	High-performance liquid chromatography
ID	Internal diameter
IS	Internal standard
L	Liter
LOD	Limit of detection or some other description indicating that this is the smallest concentration or quantity that can be detected or analyzed for
LOQ	Lower limit of quantitation, either given as such in the paper or taken as the lower limit of the linear quantitation range
M	Molar (i.e., moles/L)
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
mL	Milliliter
mM	Millimolar (i.e., millimoles/L)
MS	Mass spectrometric detection
MSPD	Matrix solid phase dispersion
MTBE	Methyl tert-butyl ether
nM	Nanomolar (i.e., nanomoles/L)
psi	Pounds/sq. in. (1 psi = 6.89476 kPa)
s	Seconds
SEC	Size Exclusion Chromatography
SFC	Supercritical fluid chromatography
SFE	Supercritical fluid extraction
SPE	Solid phase extraction
Temp	Temperature
U	Units
UV	Ultraviolet detection
vol	Volume

PIC REAGENTS

These reagents are offered by Waters as buffered solutions containing the following compounds:

PIC A is tetrabutylammonium sulfate

PIC B5 is pentanesulfonic acid

PIC B7 is heptanesulfonic acid.

WORKING PRACTICES

In general, good working practice, for example, using high-grade materials is assumed. Solutions should be protected from light, and silanized glassware should be used unless you have good reason to believe that these precautions are not necessary. Details of solution preparation are generally not given. It should be remembered that the preparation of a dilute aqueous solution of a relatively water-insoluble compound can frequently be made by dissolving the compound in a small volume of a water-miscible organic solvent and diluting this solution with water. A number of excellent texts³⁻⁹ discuss good working practices and procedures in HPLC. Please note that all the temperatures are in degrees C.

It is also assumed that safe working practices are observed. Organic solvents should only be evaporated in a properly functioning chemical fume hood, correct protective equipment should be worn when dealing with potentially hazardous biological materials, and waste solutions should be disposed of in accordance with all applicable regulations.

A number of solvents are particularly hazardous. For example, benzene is a human carcinogen;¹⁰ chloroform,¹¹ dichloromethane,¹² dioxane,¹³ and carbon tetrachloride¹⁴ are carcinogenic in experimental animals; and DMF¹⁵ and MTBE^{16,17} may be carcinogenic. Organic solvents are, in general, flammable and toxic by inhalation, ingestion, and skin absorption. Sodium azide is carcinogenic and toxic and liberates explosive, volatile, toxic hydrazoic acid when mixed with acid. Sodium azide can form explosive heavy metal azides, for example, with plumbing fixtures, and so should not be discharged down the drain.¹⁸ Disposal procedures have been described for a number of hazardous drugs and reagents,¹⁸ and a procedure for the hydrolysis of acetonitrile in waste solvent to the much less toxic acetic acid and ammonia^{19,20} has been described. *n*-Hexane is surprisingly toxic.²¹

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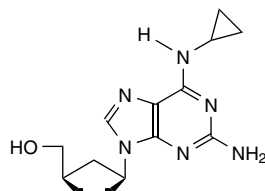
Abacavir

Molecular formula: C₁₄H₁₈N₆O

Molecular weight: 286.33

CAS Registry No: 136470-78-5 (base), 188062-50-2 (sulfate)

Merck Index: 13,1



SAMPLE

Matrix: blood

Sample preparation: Condition a 1 mL 100 mg Bond Elut-C SPE cartridge with 1 mL MeOH and 1 mL 100 mM pH 7.0 ammonium acetate buffer. Heat plasma at 58° for 1 h to inactivate HIV. Vortex 800 µL plasma with 300 µL 2 µg/mL hexobarbital in 25 mM pH 7.0 ammonium acetate buffer for 30 s and centrifuge at 18 000 g for 5 min. Add 1 mL of the supernatant to the SPE cartridge, wash with 1 mL 100 mM pH 7.0 ammonium acetate buffer, suck dry for 1 min, elute with 800 µL MeOH. Evaporate the eluate to dryness under a stream of nitrogen at 40° and reconstitute the residue with 100 µL mobile phase. Vortex for 30 s, centrifuge at 18 000 g for 3 min, and inject an 80 µL aliquot.

HPLC VARIABLES

Guard column: 20 × 3.9 5 µm Polarity dC18 (Waters)

Column: 150 × 3.9 5 µm Polarity dC18 (Waters)

Column temperature: 40

Mobile phase: Gradient. A was 10 mM pH 6.5 ammonium acetate buffer. B was 10 mM pH 6.5 ammonium acetate buffer:MeCN:MeOH 20:50:30. A:B 96:4 for 15 min, to 36:64 over 15 min, maintain at 36:64 for 3 min, re-equilibrate at initial conditions for 7 min.

Flow rate: 1.1

Injection volume: 80

Detector: UV 269 for 11 min, UV 250 for 3 min, UV 271 for 10 min, UV 230 for 9 min

CHROMATOGRAM

Retention time: 25.1

Internal standard: hexobarbital (30.6)

Limit of quantitation: 10.0 ng/mL

OTHER SUBSTANCES

Extracted: didanosine (13.6), lamivudine (8.6), nevirapine (27.3), stavudine (15.7), zalcitabine (5.9), zidovudine (23.8)

Noninterfering: tenofovir

KEY WORDS

plasma; SPE

REFERENCE

Rezk, N.L.; Tidwell, R.R.; Kashuba, A.D.M. Simultaneous determination of six HIV nucleoside analogue reverse transcriptase inhibitors and nevirapine by liquid chromatography with ultraviolet absorbance detection, *J.Chromatogr.B*, **2003**, 791, 137–147.

SAMPLE

Matrix: blood

Sample preparation: Condition a 100 mg Dual Zone C18 SPE cartridge (Diazem) with 2 mL MeOH and 2 mL water. Dilute 500 µL serum with 1 mL water, add to the SPE cartridge, wash with 500 µL water, elute with 1 mL MeOH. Evaporate the eluate to

dryness with vortexing under reduced pressure at 40° and reconstitute the residue with 300 µL MeOH, inject a 10 µL aliquot.

HPLC VARIABLES

Column: two 150 × 4.6 3 µm Luna C18 columns in series

Column temperature: 60

Mobile phase: Gradient. MeCN:water from 5:95 to 45:55 over 20 min.

Flow rate: 0.85

Injection volume: 10

Detector: UV 250

CHROMATOGRAM

Retention time: 17

Limit of detection: 75 ng/mL

OTHER SUBSTANCES

Extracted: didanosine (10.5, LOD 120 ng/mL), lamivudine (9.5, LOD 260 ng/mL), stavudine (11.5, LOD 40 ng/mL), zalcitabine (7.5, LOD 440 ng/mL), zidovudine (16, LOD 30 ng/mL)

KEY WORDS

SPE; serum

REFERENCE

Simon, V.A.; Thiam, M.D.; Lipford, L.C. Determination of serum levels of thirteen human immunodeficiency virus-suppressing drugs by high-performance liquid chromatography, *J.Chromatogr.A*, **2001**, *913*, 447–453.

SAMPLE

Matrix: blood

Sample preparation: Mix 300 µL plasma with 75 µL 20% perchloric acid for 30 s, centrifuge at 1300 g for 15 min, inject a 100 µL aliquot.

HPLC VARIABLES

Guard column: 20 × 3.8 Symmetry C18 (Waters)

Column: 100 × 4.6 3.5 µm Symmetry C18 (Waters)

Column temperature: 41 ± 2

Mobile phase: MeCN:25 mM pH 7.0 phosphate buffer 15:85

Flow rate: 1

Injection volume: 100

Detector: UV 285

CHROMATOGRAM

Retention time: 4.8

Limit of quantitation: 20 ng/mL

OTHER SUBSTANCES

Simultaneous: didanosine, folic acid, ganciclovir, lamivudine, nevirapine, pyrazinamide, ranitidine, rifampin, stavudine, sulfamethoxazole, trimethoprim, zidovudine

Noninterfering: adefovir, amprenavir, delavirdine, efavirenz, fluconazole, indinavir, itraconazole, methadone, nelfinavir, oxazepam, pyrimethamine, rifampin, ritonavir, saquinavir, zalcitabine

KEY WORDS

plasma

REFERENCE

Veldkamp, A.I.; Sparidans, R.W.; Hoetelmans, R.M.W.; Beijnen, J.H. Quantitative determination of abacavir (1592U89), a novel nucleoside reverse transcriptase inhibitor, in human plasma using isocratic reversed-phase high-performance liquid chromatography with ultraviolet detection, *J.Chromatogr.B*, **1999**, 736, 123–128.

SAMPLE

Matrix: blood

Sample preparation: Centrifuge plasma at 4000 g for 20 min using a Centrifree micropartition device (Amicon), inject a 100 μ L aliquot of the ultrafiltrate.

HPLC VARIABLES

Column: 250 \times 4.6 Adsorbosphere C18

Mobile phase: Gradient. A was MeCN:water 80:20. B was 50 mM ammonium acetate containing 0.1% triethylamine adjusted to pH 5.5. A:B from 0:100 to 50:50 over 30 min, re-equilibrate at initial conditions for 10 min.

Flow rate: 1

Injection volume: 100

Detector: UV 260, UV 285

CHROMATOGRAM

Retention time: 23

OTHER SUBSTANCES

Extracted: carbovir (20)

KEY WORDS

rat; pharmacokinetics; plasma

REFERENCE

Daluge, S.M.; Good, S.S.; Faletto, M.B.; Miller, W.H.; St.Clair, M.H.; Boone, L.R.; Tisdale, M.; Parry, N.R.; Reardon, J.E.; Dornisfe, R.E.; Averett, D.R.; Krenitsky, T.A. 1592U89, a novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity, *Antimicrob.Agents Chemother.*, **1997**, 41, 1082–1093.

SAMPLE

Matrix: CSF, urine

Sample preparation: Centrifuge CSF or urine at 12 000 g for 5 min, dilute a 75 μ L aliquot to 750 μ L with mobile phase, inject an aliquot.

HPLC VARIABLES

Column: 150 \times 3.2 5 μ m Kromasil C18 (Phenomenex)

Mobile phase: Gradient. MeOH:25 mM pH 4.0 ammonium acetate buffer from 5:95 to 50:50 over 30 min, re-equilibrate at initial conditions for 10 min.

Flow rate: 0.7

Detector: UV 295

CHROMATOGRAM

Retention time: 25.5

Limit of quantitation: 62 ng/mL (CSF), 629 ng/mL (urine)

OTHER SUBSTANCES

Extracted: metabolites, abacavir 5'-glucuronide, abacavir 5'-carboxylate

REFERENCE

Ravitch, J.R.; Moseley, C.G. High-performance liquid chromatographic assay for abacavir and its two major metabolites in human urine and cerebrospinal fluid, *J.Chromatogr.*, **2001**, 762, 165–173.

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