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Analytical Methods in the Quality Control of Scientific Publications Part II: The Authors', Reviewers', Editors' Responsibility, and the Publishers' Authority

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ABSTRACT

Publication of scientific documents as research reports and original papers has an important place in displaying the authors' knowledge, integrity, responsibility, and honesty. The same is true for the reviewers and editors. The authority of a publisher strongly depends on the qualifications of the experts who review the manuscripts, and the recommendations they provide to the authors and editors. The honesty of the authors, reviewers, and editors is of the utmost importance. The author of the paper titled "Analytical Methods in Quality Control of Scientific Publications", which was published in the *American Journal of Analytical Chemistry*, 2012, 3, 443-447 (DOI: 10.4236/ajac.2012.36058) had criticized the paper published by Dongre *et al*., "Application of GC-EI-MS for the Identification and Investigation of Positional Isomer in Primaquine, an Antimalarial Drug," *Journal of Pharmaceutical and Biomedical Analysis*, 2005, 39, 111-116 (DOI: 10.1016/j.jpba.2005.03.019), for presenting falsifications in this publication. Neither the reviewer nor the Editor-in-Chief Bezhan Chankvetadze of the *Journal of Pharmaceutical and Biomedical Analysis* has reacted to accusations of falsification. If a reviewer and editor are poorly qualified, unprincipled, or even corrupt, as was suggested by Bob Grant in *The Scientist* magazine (http://www.the-scientist.com/display/55679/#ixzz0mmsPoMIS), it is not good enough to consider simply that the publisher/journal has a high ranking and is indexed in PubMed or the Institute for Scientific Information (ISI). In this editorial, we report a profound misunderstanding or a lack of knowledge by the authors Shixue G., Zhuoyu L., and Wei W., in their paper published in ZhongguoYaoye *China Pharmaceuticals*, Vol. 14, No. 4, 2005, pp. 36-37 and a similar lack of professionalism by reviewers and editors. The influence and the role of internationally used pharmacopeias, such as The British Pharmacopoeia, European Pharmacopoeia, The United States Pharmacopeial Convention, and United States Pharmacopeia are shown as the main initiators and drivers of these misunderstandings.

Keywords: Primaquine; Isomers; Enantiomers; TLC; Spurious Publications; Pharmacopeias

1. Historic Perspective of the Problem

Every scientist in chemistry and every chemistry student know that the water is H_2O and all the molecules are of the same composition and character and have the same chemical properties. The same ideas can be applied to methanol, glucose, and millions and millions of distinct chemical substances. No one refers to water as "water and related substances". However, this was not applicable to primaquine as a description by the members of international pharmacopeia committees. The decision of pharmacopeia committees concerning primaquine was that primaquine is "primaquine and related substances" [1-7]. In this editorial, we report a profound misunderstanding in paper published by the authors Shixue G., Zhuoyu L., and Wei W. [8], who claimed to resolve primaquine enantiomers using TLC without transforming the enantiomers to diastereomers or to a diastereomeric transitional state.

2. Primaquine

What meant by the "related substances" in terms of primaquine? How they related? Are the substances the degradation products produced during shelf life (storage), or are they byproducts of primaquine synthesis, remaining

unreacted reagents, or something else? The members of pharmacopeia committees were diffidently silent on this issue. Primaquine phosphate [1] slowly transforms to become primaquine diphosphate [9], and later to primaquine bis-phosphate. Primaquine has also been qualified as primaquine and its enantiomer [10]; however, it appears to have been never straightforwardly and openly stated that primaquine has been contaminated with significant proportions of a toxic substance known as quinocide and should be classified as primaquine and quinocide. Quinocide was found in primaquine as long ago as 1997 as shown in document **Figure 1** and described in publications [11-14].

Primaquine is a mixture of two enantiomers of primaquine and two enantiomers of quinocide. These enantiomers are found in raw ware primaquine; the mixture is optical active and as such is not racemic. This is shown in **Figure 2**.

In primaquine, the proportions of contaminants at the time of discovery of the contaminant quinocide in (1997-1998) were from 10% in low quality samples to 6.5% in the highest quality samples, but never less than 6%. **Figure 3** is a copy of the original documents for the routine analysis of commercial raw ware primaquine. This analysis was reported by an analytical laboratory, Weifa AS, Oslo, Norway.

In this document, the total contamination level was recorded at over 8%.

The unexplained *definition* of "related substances" has brought to light a lot of speculations. To date, pharmacopeia committees appear to have resisted recognizing the presence of contamination of primaquine with the defined chemical and toxic substance quinocide, which exceeded accepted norms for a single known contaminant. An example of the definition given in the United States Pharmacopeia (USP) [15] is reproduced in **Figure 4**.

What is the primaquine related compound A[a] 8-[(4-aminopentyl) amino]-6-methoxyquinoline? In what way or manner is primaquine, which is *N*-(6-methoxyquinolin-8-yl)pentane-1,4-diamine related to 8-[(4-aminopentyl) amino]-6-methoxyquinoline?

How is primaquine related to 8-[(4-aminopentyl) amino]-6-methoxyquinoline as shown in **Figure 5**? The recognition of single and defined contaminant or "specified unidentified impurity" at this magnitude should lead to the demand for the requalification of the permitted amount of contamination in primaquine or acceptance of the high level of contamination with a single known contaminant in other drugs. It is not a case with the "related substance". However, according to this table from a USP publication [15] quinocide is present in primaquine at NMT 2%, despite the fact that approximately 3% of this substance was present in nearly all raw unprocessed primaquine used in the pharmaceutical industry before. Is this reduction because of the changes and use at presence new synthesis procedure for primaquine?

There are general rules for permitted amounts of a single known contaminant in pharmaceutical preparations. If these rules are followed, the pharmaceutical industry will lose significant income, which this industry receives by launching improper products (with single contaminant about 2%) as primaquine with the apparent blessings of pharmacopeia committees.

Knowledge of the contamination of primaquine with quinocide has been available since 1997. We had many problems to overcome before we could break barriers to present this information in 2003 [11]. The pharmaceutical industry and pharmacopeia committees put obstacles in the way of obtaining this information. Globally, the pharmaceutical industry, pharmaceutical authorities, and pharmacopeia committees conducted a circus performance, the circus of "non-recognition the fact of contamination of primaquine with quinocide". The Chongqing Institute for Drug Control was no exception to the rule [8]. At present, other circus performances are taking place: "the non-information about the toxic abilities of the mixture of 8-[(4-aminopentyl)amino]-6-methoxyquinoline with primaquine."

3. Isomers and Isomerism

In organic chemistry, there are several million different compounds, but most of them are composed of very few elements: C, H, O, N, S, halides, and more rarely, several metals. A chemical formula presents the substance by composition of these elements qualitatively and quantitatively, for example: C_4H_{10}. The formula, or as it is called, the empirical formula for this substance can represent *n*-butane. However, two different substances with this empirical formula exist, (normal) *n*-butane and 2-methylpropane. In isomers, the elements are commonly found in the same number in chemical formulae, but are connected in various different ways. The carbon atoms in each of these substances are connected to each other in a different way. The connection of carbon atoms in a molecule is shown by the structural formula. The structural formulae of both *n*-butane and 2-methylpropane are shown in **Figure 6**.

Different compounds that have the same empirical, molecular formula are "empirical formula isomers". Two empirical formula isomers can also be the constitutional isomers. Primaquine and quinocide are shown in **Figure 7**. They are also empirical formula and constitutional isomers at the same time.

Constitutional isomers are isomers that differ in the order in which their atoms are connected, and are also known as "structural isomers". The formal definition of constitutional isomers is "compounds that have the same molecular formula and different connectivity".

Because carbon atoms have a valence of four, they can

WEIDERS FARMASØYTISKE A/S

I. Brondz (Kopi)
23/5 c

TGA
Therapeutic Goods Administration
PO Box 100 Woden ACT
2606 Australia

DERES REF VAR REF HSch/ra OSLO 27 April 1998

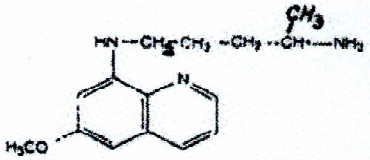
Dear Sirs,

REGARDING: PRIMACIN™ - PRIMAQUINE TABLETS 7.5MG;
Reg. no. AUST R 63856.

A typical sample of Primaquine Phosphate substance manufactured by the Chinese manufacturer ZhongXi, has been analyzed by Dr. Ilia Brondz at the University of Oslo, Norway.

Using GC-MS technique, he has found that the major impurity in this Primaquine Phosphate quality is a geometric isomer of primaquine, most probably also present as a phosphate.

He has also found that it is most probably a side chain isomer of primaquine, the structure of which is shown below:



Based upon routes of synthesis published in the literature the presence of this isomer in the primaquine quality is likely.

This isomer has probably been present in Primaquine Phosphate substance for a number of years. The similarity in structure between the two isomers, makes it likely that there is no major differences in toxicological properties although no proof has been established.

We kindly ask that this information is kept confidential until dr. Ilia Brondz has had the possibility to publish these results in an international journal.

Yours sincerely,
Weiders Farmasøytiske A/S

Johan Røe
Chief Chemist

Henrik Schultz
Director of Research

Copy: Boucher & Muir PTY LTD

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Figure 1. The contamination of primaquine by quinocide has been publicly known since April 1998.

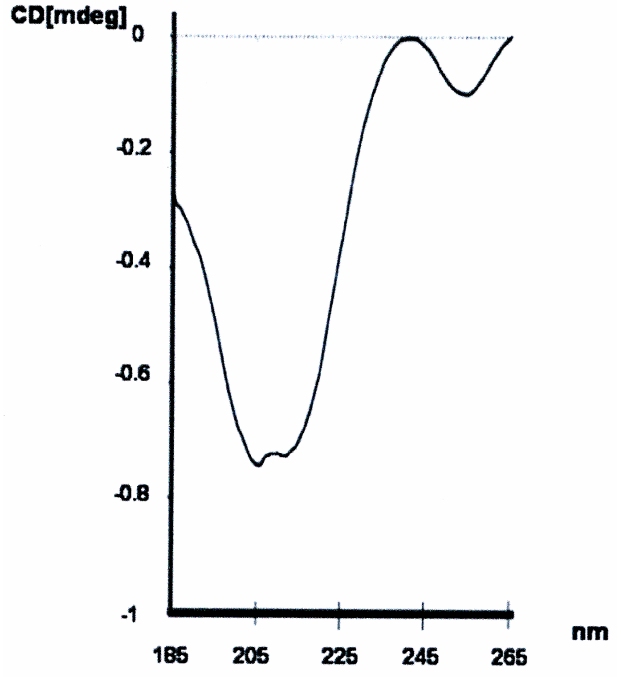


Figure 2. A solution of raw ware primaquine used in industry. Primaquine is optically active and not racemic. The CD analysis demonstrated this [14].

be connected to four other different atoms. Valences can be visually placed at the corners of a tetrahedron; such constructions are symmetric if all corners of the tetrahedron are occupied by atoms of the same type and can be superimposed or asymmetric if the four corners are occupied by different atoms and cannot be superimposed, as shown in **Figure 8**. This is also true if the atoms are changed to functional groups or other substituents. The carbon in molecules in **Figure 8** is known as an asymmetric or chiral carbon. Solutions of molecules containing a chiral carbon in their structure have the property of being able to rotate the plane of polarized light. Two molecules with different spatial locations of different atoms around carbon are stereoisomers. Enantiomers are two stereoisomers that are related to each other by a mirror reflection: they are mirror images of each other, which are non-superimposable. Two enantiomers are shown in **Figure 8**.

Enantiomers in **Figure 8**, by contrast with isomers in **Figure 7**, have the same physicochemical properties such as melting point, boiling point, and solubility, with the exception of rotating a plane of polarized light in opposite directions. If, when in solution, all molecules of the enantiomer rotate the plane of polarized light in a clockwise direction they are described as the (+)-enantiomer. If, when in solution all molecules of the enantiomer rotate the plane of polarized light in a counterclockwise direction they are described as the (–)-enantiomer. The angle of the rotation of a plane of polarized light by each molecule of an enantiomer pair has the same magnitude, but different direction. The enantiomers crystalize as right or left crystals depending on the sign of the enantiomer. Enantiomer molecules of different signs of rotation have different reactivity toward enzymes and biological systems.

4. Diastereomers

There are a number of other isomers; however, it is of interest here to understand that diastereomers are isomers with two chiral carbons in their molecules as shown in **Figure 9**.

Two diastereomers respectively, have different physicochemical properties such as melting point, boiling point, and solubility. They are also can be optically active; a solution of diastereomers can rotate a plane of polarized light.

5. Mixture of Enantiomers

In nature, because of stereospecific synthesis involving enzymes, as a rule all molecules that are formed by primary synthesis have a common stereochemistry. In biology, adopted nomenclature for the chiral carbons is levo (L-) and dextro (D-). All naturally occurring amino acids in proteins belong to the L-stereo chemical series. It is possible to find amino acids with D-chirality; however, this is because of secondary metabolic transformation. “Enantiomer” is the modern term for “optical isomer.” In industrial synthesis, stereospecific synthesis is seldom used. It is usual to use nonstereospecific synthesis. Therefore, industrial synthesis usually results in a mixture of enantiomers. A solution of 50% (+)-enantiomers and 50% of (–)-enantiomers does not rotate plane polarized light. The solution is called optically inactive or racemic, or a simple “racemate”. A solution in which one of the enantiomer presented in excess, but not to the exclusion of the other, is called “enantioenriched”.

However, the (+)/(–) system has no fixed relationship with the (*R*)/(*S*) system. Optical activity is easy to measure, but advanced equipment is needed to decide whether a molecule has an *R* or *S* configuration. Pharmacopeia committees broadly and heavily misuse this point.

6. Enantiomer Resolution (Chiral Resolution)

Several different techniques are used to separate substances. One of the techniques is chromatography. The separation of enantiomers by chromatography is called “resolution of enantiomers” or “chiral resolution”, or simply “resolution”. The chromatography technique is mainly based on the physicochemical properties of molecules.

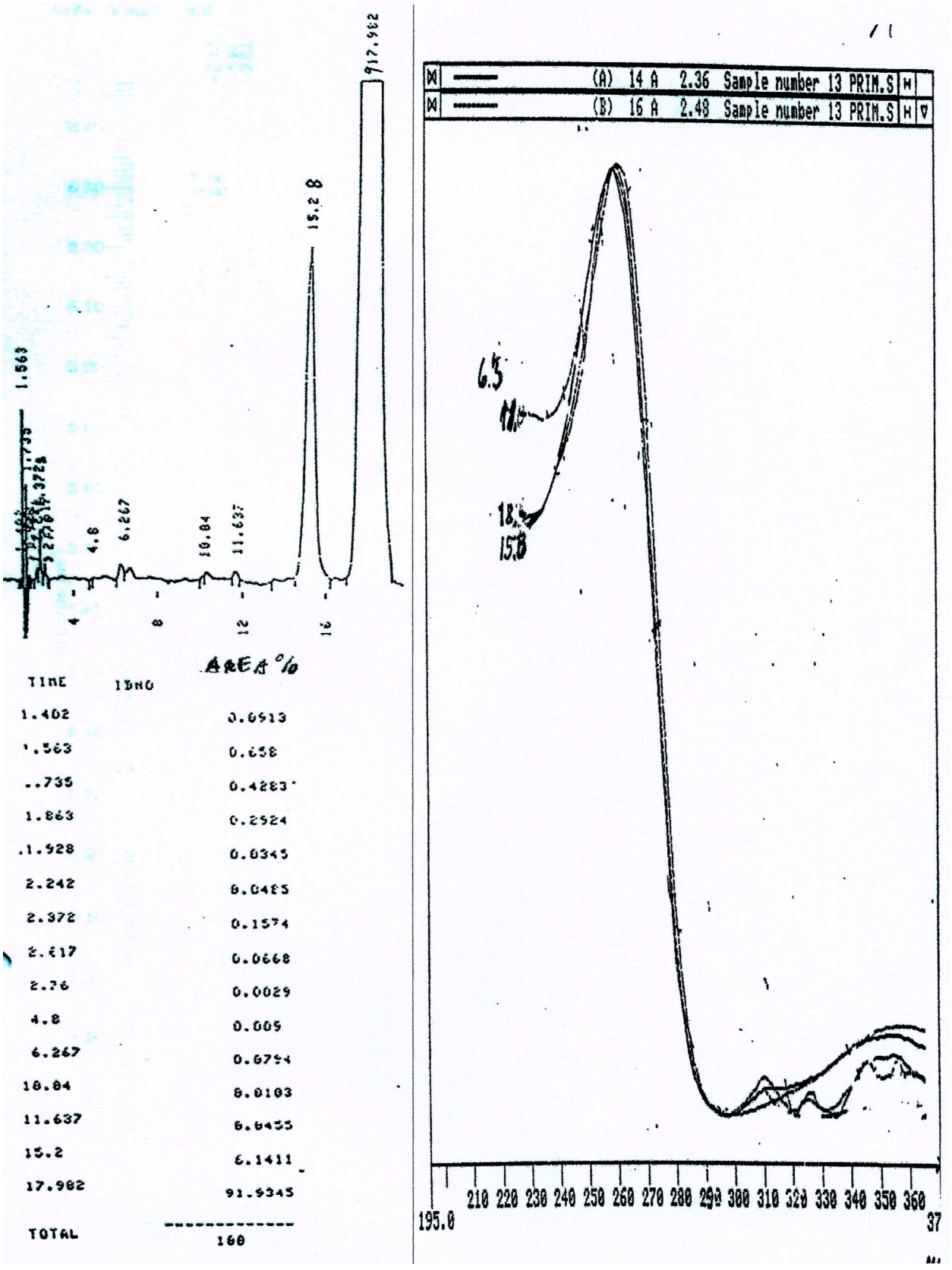


Figure 3. The document from routine laboratory analysis at Weifa AS, Oslo, Norway shows more than 8% contamination with quinocide. The primaquine content in the raw ware is less than 92%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Specified unidentified impurity	0.24	0.20
Specified unidentified impurity	0.29	0.60
Primaquine related compound A[a]	0.80	2.0
Primaquine	1.0	—
Specified unidentified impurity	1.8	0.50 (RB 1-Jan-2012)
Any other individual impurities	—	0.20
Total impurities	—	3.0

[a] 8-[(4-Aminopentyl)amino]-6-methoxyquinoline.

Figure 4. There are USP qualitative and quantitative descriptions of the composition of primaquine. Abbreviation NMT is general notices and requirements in US Pharmacopeial Convention standing for "not more than".

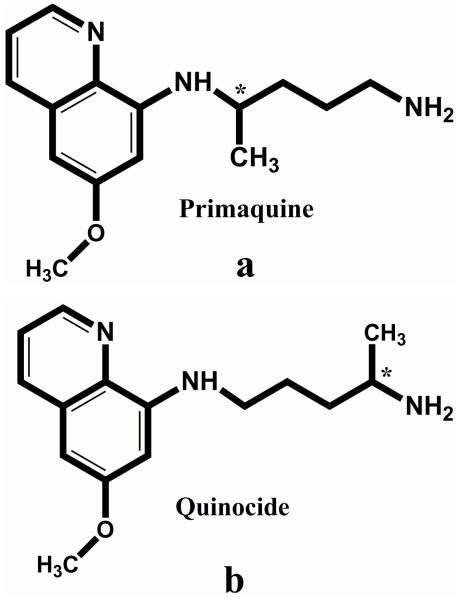


Figure 5. (a) Primaquine; (b) Quinocide 8-[(4-aminopentyl) amino]-6-methoxyquinoline.

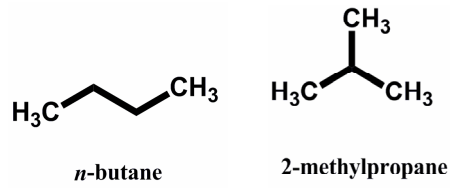
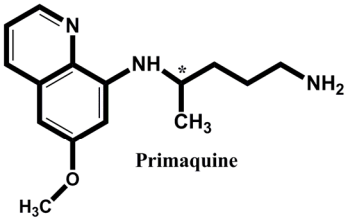
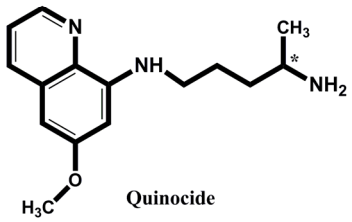


Figure 6. The structural formulae of both *n*-butane and 2-methylpropane.

Isomers that have distinct differences in melting point, boiling point, or solubility can be separated by chromatographic methods. However, enantiomers have the same physicochemical properties and cannot be separated by traditional chromatography. Nevertheless, chromatographic separation or so-called resolution can be performed by chromatography for enantiomers. Chromatography resolution of enantiomers is based on the fact that diastereomers have different physicochemical properties such as melting point, boiling point, or solubility. Three main approaches are used. 1) A synthetic reaction of a



Title: Primaquine
CAS Registry Number: 90-34-6
CAS Name: N4-(6-Methoxy-8-quinolinyl)-1,4-pentanediamine
Additional Names: 8-(4-amino-1-methylbutylamino)-6-methoxyquinoline
Manufacturers' Codes: SN-13272
Molecular Formula: C15H21N3O Molecular Weight: 259.35
Percent Composition: C 69.47%, H 8.16%, N 16.20%, O 6.17%
Boiling point: bp 175-179°C

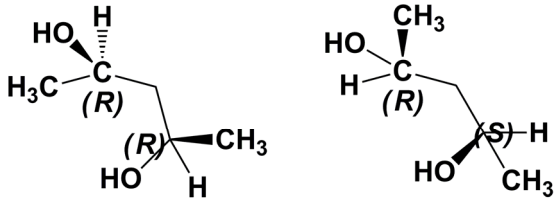


Title: Quinocide
CAS Registry Number: 525-61-1
CAS Name: N1-(6-Methoxy-8-quinolinyl)-1,4-pentanediamine
Additional Names: 8-(4-aminopentylamino)-6-methoxyquinoline; 8-[(4-amino-4-methylbutyl)amino]-6-methoxyquinoline; 6-methoxy-8-(4-aminopentylamino)quinoline; chinocide; khinocyde
Molecular Formula: C15H21N3O Molecular Weight: 259.35
Percent Composition: C 69.47%, H 8.16%, N 16.20%, O 6.17%
Properties: bp 183-186°C Melting point: mp 46°C

Figure 7. The two constitutional isomers: primaquine and quinocide.

(*S*)-bromochlorofluoromethane (*R*)-bromochlorofluoromethane

Figure 8. Enantiomers are two stereoisomers that are related to each other by a mirror reflection.



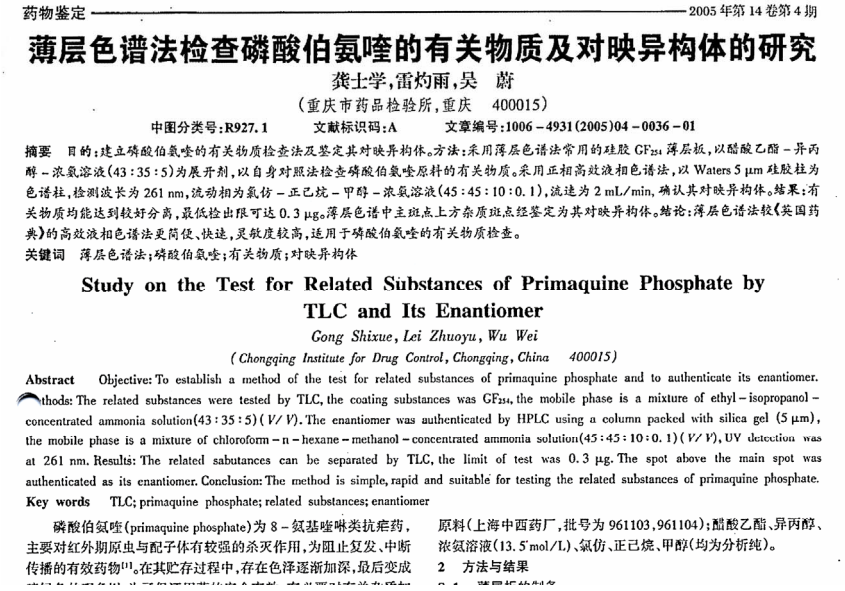
(2*R*,4*R*)-pentane-2,4-diol (2*R*,4*S*)-pentane-2,4-diol

Figure 9. Two diastereomers.

mixture of a pair of enantiomers with an optically active isomer. The demands of the reaction are that the products become diastereomers and that diastereomers can be decomposed to the initial enantiomers and an additional product (optically active substance). 2) The enantiomers and an optically active substance in solution (mobile phase) compose a transitional diastereomeric state and this transitional state is easy decomposed into initial reagents. The specific substance in the mobile phase, which is called a "chiral selector", is an optically active substance. 3) The use of an "enantio-/chiral support" or "enantio-/chiral stationary phase"; which, under chromatographic conditions, forms a transitional diastereomeric state with enantiomers. The transitional diastereomeric state is in mass balance with the reactants. The reactants (enantiomer stationary phase/enantiomers in solution) will be composed and decomposed during the chromatographic process. In all of these approaches, the transformation of a mixture of a pair of enantiomers to the mixture of diastereomers is needed for resolution. An enantiomer mixture without these processes cannot be resolved.

7. Is It "A New Method to Resolve Enantiomers on TLC" without Transforming the Enantiomers to Diastereomers or to a Diastereomeric Transitional State?

The publication by Shixue *et al*. [8], (the part of text presented in **Figure 10)** describes a *groundbreaking* discovery, which can be summarized as separation of sub-



药物鉴定 2005 年第 14 卷第 4 期

薄层色谱法检查磷酸伯氨喹的有关物质及对映异构体的研究

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中图分类号:R927.1 文献标识码:A 文章编号:1006-4931(2005)04-0036-01

摘要 目的:建立磷酸伯氨喹的有关物质检查法及鉴定其对映异构体。方法:采用薄层色谱法常用的硅胶 GF_{254} 薄层板,以醋酸乙酯-异丙醇-浓氨溶液(43:35:5)为展开剂,以自身对照法检查磷酸伯氨喹原料的有关物质。采用正相高效液相色谱法,以 Waters 5 μm 硅胶柱为色谱柱,检测波长为 261 nm,流动相为氯仿-正己烷-甲醇-浓氨溶液(45:45:10:0.1),流速为 2 mL/min,确认其对映异构体。结果:有关物质均能达到较好分离,最低检出限可达 0.3 μg。薄层色谱中主斑点上方杂质斑点经鉴定为其对映异构体。结论:薄层色谱法较《英国药典》的高效液相色谱法更简便、快速,灵敏度较高,适用于磷酸伯氨喹的有关物质检查。

关键词 薄层色谱法;磷酸伯氨喹;有关物质;对映异构体

Study on the Test for Related Substances of Primaquine Phosphate by TLC and Its Enantiomer

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(Chongqing Institute for Drug Control, Chongqing, China 400015)

Abstract Objective: To establish a method of the test for related substances of primaquine phosphate and to authenticate its enantiomer. Methods: The related substances were tested by TLC, the coating substances was GF_{254}, the mobile phase is a mixture of ethyl-isopropanol-concentrated ammonia solution(43:35:5)(*V/V*). The enantiomer was authenticated by HPLC using a column packed with silica gel (5 μm), the mobile phase is a mixture of chloroform-n-hexane-methanol-concentrated ammonia solution(45:45:10:0.1)(*V/V*), UV detection was at 261 nm. Results: The related sabutances can be separated by TLC, the limit of test was 0.3 μg. The spot above the main spot was authenticated as its enantiomer. Conclusion: The method is simple, rapid and suitable for testing the related substances of primaquine phosphate.

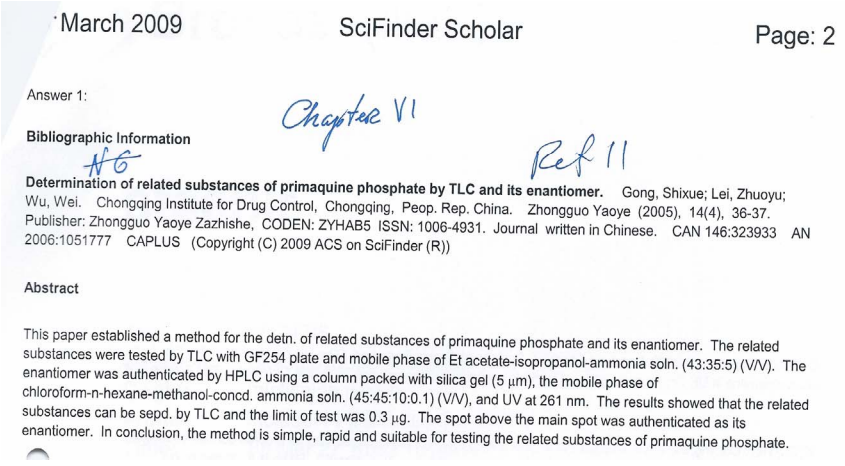
Key words TLC; primaquine phosphate; related substances; enantiomer

磷酸伯氨喹(primaquine phosphate)为 8-氨基喹啉类抗疟药,主要对红外期原虫与配子体有较强的杀灭作用,为阻止复发、中断传播的有效药物[1],在其贮存过程中,存在色泽逐渐加深,最后变成

原料(上海中西药厂,批号为 961103,961104);醋酸乙酯、异丙醇、浓氨溶液(13.5 mol/L)、氯仿、正己烷、甲醇(均为分析纯)。

2 方法与结果

(a)



March 2009 SciFinder Scholar Page: 2

Answer 1:

Chapter VI

Bibliographic Information

NG

Ref 11

Determination of related substances of primaquine phosphate by TLC and its enantiomer. Gong, Shixue; Lei, Zhuoyu; Wu, Wei. Chongqing Institute for Drug Control, Chongqing, Peop. Rep. China. Zhongguo Yaoye (2005), 14(4), 36-37. Publisher: Zhongguo Yaoye Zazhishe, CODEN: ZYHAB5 ISSN: 1006-4931. Journal written in Chinese. CAN 146:323933 AN 2006:1051777 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Abstract

This paper established a method for the detn. of related substances of primaquine phosphate and its enantiomer. The related substances were tested by TLC with GF254 plate and mobile phase of Et acetate-isopropanol-ammonia soln. (43:35:5) (V/V). The enantiomer was authenticated by HPLC using a column packed with silica gel (5 μm), the mobile phase of chloroform-n-hexane-methanol-concd. ammonia soln. (45:45:10:0.1) (V/V), and UV at 261 nm. The results showed that the related substances can be sepd. by TLC and the limit of test was 0.3 μg. The spot above the main spot was authenticated as its enantiomer. In conclusion, the method is simple, rapid and suitable for testing the related substances of primaquine phosphate.

(b)

Figure 10. (a) The text described resolution of enantiomers without selectors on non-chiral phase is the part of text from original journal; (b) The text below is text from Web SciFinder Scholar.

stances related to primaquine and its enantiomer that was achieved by using TLC and HPLC with mobile phases, without selectors, and on a silica based support/stationary phase (achiral phase). Most interesting in this *discovery* was the authentication of a spot as an enantiomer to primaquine. The spot was separated from primaquine and was above the primaquine spot on the TLC plate. The spot was presented as an authentic enantiomer of primaquine.

Without a doubt, the results of this outstanding discovery were directly inspired by publication of information in pharmacopoeias [6,7,9] and in the other outstanding scientific publications of authoritative power. How could a simple pharmaceutical analyst stand against the "*Bibles of Pharmacy*?" The qualifications of the leading scientists in the Chongqing Institute of Drug Control Committee, Chongqing, 400015, China who recognized and allowed publication of these results are not clear. However, of most interest is in the absence of reactions from the reviewers and editor of *China Pharmaceuticals*. How could this paper be published in a *serious* journal?

My personal opinion is that members of pharmacopoeia committees have guarded the pharmaceutical industry by concealing knowledge about the presence of other substance such as quinocide as a contaminant in primaquine by presenting the contaminant as related substance or as enantiomer.

An interesting approach was taken in the USP [16] in which description of related substances or (*S*) and (*R*) enantiomers is omitted. Who would protest against the definition that primaquine is a (+/–)-8-[(4-amino-1-methylbutyl)amino]-6-methoxyquinoline with an empirical formula $C_{15}H_{21}N_3O$ as it defined in [16]. The analysis of primaquine was published [11-14,17-21] and as a technical note in 2006 in [17], and discussion is in progress [14,18-21].

8. Conclusions

1) Plagiarism, falsification [22], and corruption by some authors, journal editors, and reviewers, are the most important plague of scientific and professional publication [23].

2) This defect is present in all classes of publications including the highly indexed and those with high reputations.

3) A harder line should be taken against plagiarism.

4) The identity of reviewers should be known.

5) The introduction of academic editors for the review of papers is needed.

6) The exclusion of Editors-in-Chief found to have concealed falsified papers should be taken as an action by all publishers.

7) The exclusion of Editors-in-Chief guilty of corruption should be taken as an action by all publishers.

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