
ORIGINAL ARTICLE

Biomedical aspects of chiral molecules

Jiří Patočka¹ and Aleš Dvořák²

¹Department of Toxicology, Military Medical Academy, Hradec Králové and Faculty of Health and Social Studies, University of South Bohemia, České Budějovice, Czech Republic

²Lundbeck CRS, s.r.o., Praha, Czech Republic

Received 12th January 2004.

Revised 24th February 2004.

Published online 20th April 2004.

Summary

This article defines some of the terms used in chiral chemistry and some of the basic mechanistic issues that arise in stereochemistry in pharmacology. Attention is also drawn to the impact of stereochemistry on drug regulation and its significance for new drug development. The stereoselectivity of drugs is underpinned by the fact that the human body is essentially a chiral structure. The rationale for development of chiral drugs is the suggestion that single stereoisomer drugs would provide superior therapy by allowing reductions in dosage, reduced variability in metabolism and response, simpler dose-response relationships and improved tolerability.

Keywords: chiral drug – stereoisomer – enantiomer – stereochemistry – stereopharmacology

INTRODUCTION

At present almost 20 million chemical compounds are known and a number of them are the so-called isomers. Isomers in chemistry are compounds with identical molecular formulas but differing in the nature of the sequence of the bonding of their atoms in space. There are two main kinds of isomers: constitutional and stereochemical. The latent feature of all chemical compounds is their biological activity, i.e. their capability affects biochemical pathways in living organisms and influences their physiological functions. An important group of biologically active chemicals is represented by a variety of drugs and medicaments. The purpose of this article is to present general information about the chemical isomers, namely stereoisomers, the principles of chirality, the terminology used to refer to stereoisomers, and their biomedical aspects.

CONSTITUTIONAL ISOMERS

The constitution of a molecule is determined by the nature and sequence of bonding between atoms. Constitutional isomers have the same number and kinds of atoms, but differ in terms of the arrangement of atoms in the molecules. Examples of such constitutional isomers are the compounds in Table 1.

These are propanol-1, propanol-2 (isopropanol), and methyl ethyl ether. All these compounds have the molecular formula C_3H_8O but for all that, these are different individual chemicals with different chemical, physical and biological properties. Organic chemistry knows more types of isomerism (geometrical, positional, etc.) but the focus of this article is principally stereoisomerism.

STEREOCHEMICAL ISOMERS (STEREISOMERS)

These are compounds that have the same molecular formula and the same functional groups bonded in the same fashion, but which differ in the three-dimensional (3D) arrangement of their atoms or groups. The condition for the creation of a stereoisomer is the presence of at least one asymmetric carbon atom (or other four-binding

atom) in the molecule. A carbon atom is said to be asymmetric if it has four different atoms or groups attached to it. It is also said to be chiral and such an asymmetric atom is called a chiral centre. The word chiral is derived from the Greek word *cheir*, which means hand. Just like a hands, chiral molecules are not possible to match by a shift in the surface. Chiral molecules are mutually as an object and its mirror image (Fig. 1). Such space isomers are known as enantiomers. A synonym is antipodes.

Table 1. Some physical constants of three constitutional isomers of compounds with the molecular formula C_3H_8O

Compound	Structure	Specific density ($g.cm^3$)	Melting point ($^{\circ}C$)	Boiling point ($^{\circ}C$)
Propanol-1	$CH_3-CH_2-CH_2-OH$	0.804	-127	97.8
Propanol-2 (Isopropanol)	$CH_3-CH(OH)-CH_3$	0.789	-85,8	82.5
Methyl ethyl ether	$CH_3-O-CH_2-CH_3$	0.725	–	10.6

The chemical and physical properties of enantiomers are identical, except for the sign of rotation of plane-polarized light. Therefore these isomers are also known as optically active isomers. The presence of one chiral centre in a molecule gives rise to a pair of enantiomers. A mixture of both enantiomers in equal proportions is known as a racemate.

STEREOCHEMISTRY

This is a part of chemistry which treats of properties of stereoisomers (stereomers), their absolute configuration in space and their stereospecific and stereoselective reactions. Configuration is a term which refers to the relative position or order of the arrangement of atoms in space that characterizes a certain stereoisomer. The term absolute configuration refers to the actual order of the arrangement of atoms about a chiral centre. The configuration of chiral isomers can often be separated by chemical means. The number of chiral centres in a molecule can be greater than one. If there is more than one chiral centre, the yield is 2^n stereoisomers, where “n” is the number of chiral

centres and only half of the pairs are enantiomers. Isomers that are not enantiomers are called diastereomers. These have the same structural formula, but are not mirror images of one another. The chemical and physical properties of diastereomers are not usually identical. If we speak about a stereoselective reaction, we mean that only one of a set of stereoisomers is formed exclusively or predominantly. In a stereospecific reaction, a given stereoisomer leads to one product while another stereoisomer leads to a different product. All stereospecific reactions are, thus, necessarily stereoselective. The progress in stereoselective reactions, contingent on the discovery of new stereoselective catalyzators, allows the preparation of pure stereoisomers and research into their biological (pharmacological) effects.

The Nobel Prize for Chemistry in 2001 was awarded to two Americans scientists, (William S. Knowles and K. Barry Sharpless) and one Japanese (Ryoji Noyori), who created catalysts that could produce only one stereoisomer without creating the other stereoisomer. The ability to synthesize only a single isomer has opened the way to the production of chiral drugs. Chemical synthesis is no longer limited to producing racemic mixtures that contain unwanted stereoisomers.

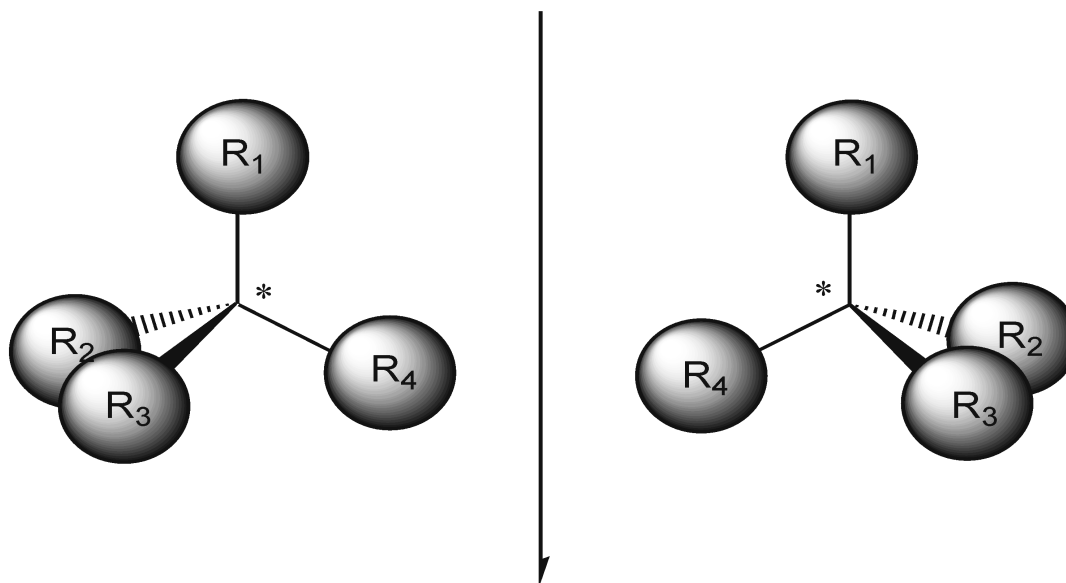


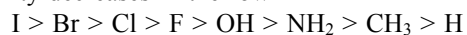
Fig. 1. **A chiral molecule has at least one chiral atom in its structure.** This is most often an atom of carbon with four different substituents (indicated here by an asterisk). If all four substituents are different, then two stereoisomers co-exist, one of which is the mirror image of the other

STEREOCHEMICAL TERMINOLOGY

The designation of different stereoisomers is somewhat complicated since there are at least three different systems to classify them and all are used more or less accidentally. The first system of stereoisomer nomenclature is the d/l or (+)/- system that is based on the direction in which the compound rotates plane-polarized light. Enantiomers that rotate plane-polarized light to the right are termed dextrarotatory which is indicated by d- or (+)- before the name of the compound, and those that rotate light to the left are termed levorotatory and are designated by a l- or (-)- prefix. A racemic mixture is indicated by either a d/l- or (+)/(-)-prefix. This system has been used in chemistry for a long time, but the rotation of plane-polarized light is not an absolute property of a compound but is rather, affected by many factors. It is generally known that the rotation depends on the solvent used. For example, a pharmacologically active stereoisomer of chloramphenicol is dextrarotatory in alcohol but levorotatory in ethyl acetate (Hutt and Tan 1996). The second system for designating enantiomers, the so called D/L-system, uses a label based on comparison to a standard reference compound, either the carbohydrate D-glyceraldehydes or the amino acid L-serine. This designation is widely used but is, however, mainly used for carbohydrates and amino acids. The third and current system of

denotation of stereoisomers is based on the sequence of atoms or groups around its chiral centre and has a conventional character. It is known as the Cahn-Ingold-Prelog system or (R,S)-system (Cahn et al. 1966). By the convention used by the International Union of Pure and Applied Chemistry (IUPAC) the two stereoisomers of a chiral compound are termed R- and S- prefix. It is the only system permitted to describe the absolute configuration of compounds which have more than one chiral centre.

The classification of the stereoisomer to R- and/or S-configuration is solved so that the groups of atoms attached to the chiral centre are arranged according to a sequence rule, in priority order of decreasing atomic number. For example, priority decreases in the row



If the atoms directly attached to the asymmetric centre are the same, the priority order is determined by the nature of the atoms further away. Multiple linkages are considered as multiple single bonds. The group of lowest priority is viewed through an imaginary triangle formed by joining the three other atoms or groups in the molecule. If the observed order of decreasing priority of the groups forming the triangle is clockwise, then the configuration is called R- which stands for rectus. If the order of decreasing priority of groups is counter-clockwise, then the configuration is called S- which stands for sinister (Fig. 2).

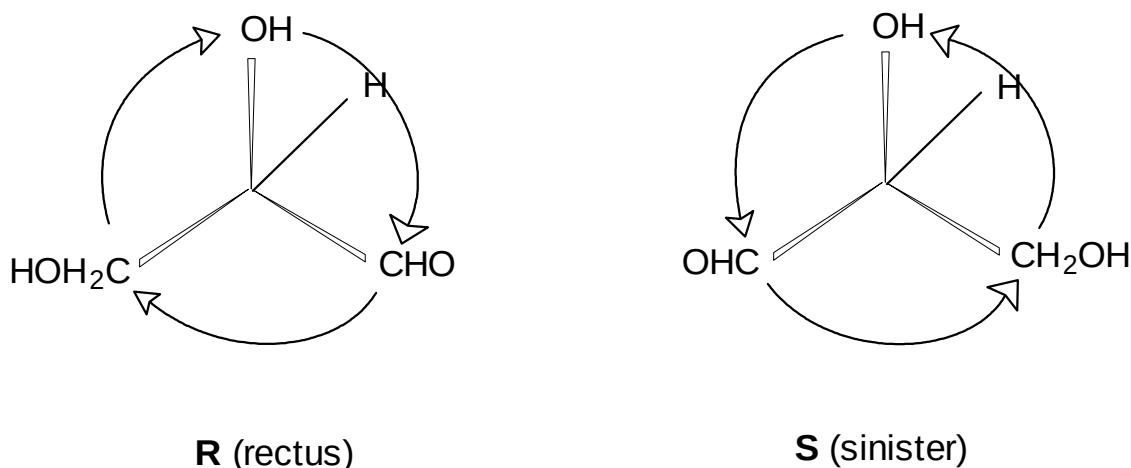


Fig. 2. **Assignment of stereochemistry of glyceraldehyde according to the Cahn-Ingold-Prelog convention.** The chiral centre is oriented with the lowest priority substituent (H in the above diagram) pointing away from eye. In glyceraldehyde, priority decreases –OH, –CHO, CH₂OH. If these three substituents in decreasing order are placed clockwise, the centre is in the R (rectus) configuration. In the anticlockwise ordering, the centre is in the S (sinister) configuration

STEREOPHARMACOLOGY

A large proportion of pharmacologically active compounds possesses a chiral centre and therefore exists in at least two stereoisomeric forms. Because the human body is essentially a chiral structure incorporating many chiral drug targets, such as enzymes, receptors and ion channels the effect is that enantiomers can have very distinct pharmacodynamic and pharmacokinetic properties that may be significant enough to translate into marked clinical differences (Ariens 1984). Only one stereoisomer of a drug molecule may fit perfectly in a chiral protein receptor, while the other may exhibit much less activity because of its inability to fit in that receptor. If we use a drug in the form of the racemate, we serve a mixture of drugs. Racemic mixtures can also be considered compounds that contain 50% impurity.

A chemical compound is said to exhibit stereospecific activity if pharmacological activity resides in only one of its stereoisomers. If pharmacological activity is found predominantly but not exclusively in one stereoisomer of the compound, it is said to have stereoselective activity. In connection with the pharmacological activities of enantiomers, two new terms have been recently used: eutomer and distomer. The eutomer is the enantiomer in which the desired effects are concentrated. The distomer is the enantiomer which is inactive or in which toxicity is concentrated. In some cases the distomer is regarded as “isomeric ballast”.

Receptor binding stereoselectivity is very often illustrated using one of our most sensitive receptor

systems – the olfactory receptors in the nose. For example R-limonene is present in oranges and is characterized by an orange odour, whereas L-limonene smells of lemons and give the characteristic odour to this fruit. Similar stereoselective distinctions can be seen in the taste and aromas of the enantiomers of other compounds. The R-enantiomer of carvone has a distinct aroma of oil of spearmint, whereas the S-enantiomer has a distinct aroma of caraway.

PHARMACOLOGICAL ACTIVITY OF ENANTIOMERS OF CHIRAL DRUGS

If one enantiomer possesses the therapeutic activity of interest (eutomer), there may be a number of different possibilities for the pharmacological activity of the second enantiomer (distomer). The term “eudesmic ratio” is the pharmacological potency ratio between the eutomer and distomer.

If the eutomer has the pharmacological activity of interest, the distomer may have: *No observable pharmacological activity*, i.e. only one of two enantiomers is pharmacologically active. The eudesmic ratio is very high and goes near infinity. It is true for example in the case of losartan, a specific angiotensin II receptor antagonist being developed as a therapeutic agent for the treatment of hypertension and heart failure.

Only its R-enantiomer is pharmacologically active (Almansa et al. 1996). Another example is citalopram, developed as an antidepressive drug. The S-citalopram inhibited serotonin transporter

functions approximately 2 times more potently than citalopram and at least 40 times more potently than R-citalopram (Sanchez et al. 2003). Citalopram was a successful product of chiral switching (Burke and Kratochvil 2002).

Weak pharmacological activity, i.e. one enantiomer is more active than the second and the eudismic ratio is greater than 1 but smaller than infinity. Warfarin is also such an example. Clinically available warfarin preparations consist of a racemic mixture of equal amounts of 2 distinct S- and R-isomers, the former being 4-times more potent as an anticoagulant and more susceptible to drug interaction (Palareti and Legnani 1996). Another example could be ibuprofen. Its S-isomer has an analgesic and anti-inflammatory effect while its R-isomer has only weak effects, but in the human body the nonactive R-isomer is converted to the active S-isomer (Cheng et al. 1994).

Antagonist activity, i.e. the distomer has a pharmacological profile other than the eutomer. For example S,R-labetalol is a strong blocker of α -adrenergic receptors while R,R-labetalol blocks β -adrenoreceptors. S,S- and R,S-isomers are inactive (Lalonde et al. 1990). On the top of this the R,R-isomer retains its hepatotoxic activity (Chon and Middleton 1992).

Diverse toxicity, i.e. one enantiomer is more toxic than the second. R-prilocaine is a safe local anaesthetic, but S-prilocaine is toxic through metabolism to o-toluidine, which induces methaemoglobulinaemia (Herdevall et al. 2003). Also the toxicity of other stereoisomers can be stereospecifically dependent, as for example the ototoxicity of the diuretic indacrinone (Rybak and Whitworth 1987) or neurotoxicity of the natural terpene thujone, and the toxic principle of flavoured distilled liquor absinthe (Patočka and Plucar 2003).

Diverse metabolism, i.e. both enantiomers are metabolised by different pathways. For example S-warfarin in humans is metabolised mainly by CYP2C9 while R-warfarin is metabolised by CYP1A2 and CYP3A4 (Pohl et al. 1976). With regard to genetic polymorphism, these have some clinical relevance (Schwarz 2003).

THERAPEUTIC PROMISE OF STEREOISOMERS

In the past two decades the opinion has prevailed that each enantiomeric drug should be considered as compound on its own merits. The effect is an increasing trend towards the development of single enantiomer drugs. Few racemates are now entering development, and there is an examination of established racemates as sources of "new" single enantiomer drugs. This tendency is known as "chiral

switch". The rationale for this trend was the suggestion that single stereoisomer drugs would provide superior therapy by allowing a reduction in dose, reduced variability in metabolism and response, simpler dose-response relationships and improved tolerability. The currently available evidence suggests that the introduction of eutomers as therapeutic agents may lead to a number of benefits, including more predictable pharmacokinetics, more accurate drug monitoring, reduced toxicity and improved tolerability. For newly developed drugs, these stereoselective characteristics are usually being elucidated early on in the drug discovery process. It allows skilled decisions on whether to proceed with the racemate or purely the enantiomer, if significant advantages exist.

CONCLUSIONS

About 25% of common drugs are racemates, i.e. mixtures of their optical or spatial isomers (stereoisomers or enantiomers). The currently available evidence suggests that for the enantiomers of many chiral drugs there are clear functional differences between the constituent enantiomers and the racemate. Frequently the enantiomers differ in their pharmacokinetics, pharmacodynamics, drug interactions and side effects. Preclinical studies suggest that a number of effective drugs already in widespread use as racemates have the potential for an improved risk/benefit ratio in enantiomeric form. Their stereospecific functional properties may be unique within a particular drug class, and may subsequently extend to the drug's clinical properties. Therefore, the pharmaceutical industry, pharmacologists and clinicians are increasingly interested in the development of enantiomers as drugs. Since advances in synthetic and analytical chemistry have provided the tools to produce stereoisomeric drugs, the authorities also recommend and support chiral switch.

REFERENCES

- Almansa C., L.A. Gomez, F.L. Cavalcanti, A.F. de Arriba, R. Rodriguez, E. Carceller, J. Garcia-Rafanell, J. Forn: Diphenylpropionic acids as new AT1 selective angiotensin II antagonists. *J. Med. Chem.* 39: 2197–2206, 1996.
- Ariens E.J.: Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. *Eur. J. Clin. Pharmacol.* 26: 663–668, 1984.

- Burke W.J., Ch.J. Kratochvil: Stereoisomers in psychiatry: the case of escitalopram. *J. Clin. Psychiatry* 4: 20–24, 2002.
- Cahn R.S., C.K. Ingold, V. Prelog: Specification of molecular chirality. *Angew. Chem.* 78: 413–447, 1966.
- Cheng H., J.D. Rogers, J.L. Demetriades, S.D. Holland, J.R. Seibold, E. Depuy: Pharmacokinetics and bioinversion of ibuprofen enantiomers in humans. *Pharm. Res.* 11: 824–830, 1994.
- Chon E.M., R.K. Middleton: Labetalol hepatotoxicity. *Ann. Pharmacother.* 26: 344–345, 1992.
- Herdevall B.M., B. Klinge, L. Persson, G. Huledal, M. Abdel-Rehim: Plasma levels of lidocaine, o-toluidine, and prilocaine after application of 8.5 g Oraqix in patients with generalized periodontitis: effect on blood methemoglobin and tolerability. *Acta Odontol. Scand.* 61: 230–234, 2003.
- Hutt A.J. and S.C. Tan: Drug chirality and its clinical significance. *Drugs* 52, Suppl. 2: 1–12, 1996.
- Lalonde R.L., T.L. O'Rear, I.W. Wainer, K.D. Drda, V.L. Herring, M.B. Bottorff: Labetalol pharmacokinetics and pharmacodynamics: evidence of stereoselective disposition. *Clin. Pharmacol. Ther.* 48: 509–519, 1990.
- Palareti G. and C. Legnani: Warfarin withdrawal. pharmacokinetic-pharmacodynamic considerations. *Clin. Pharmacokinet.* 30: 300–313, 1996.
- Patočka J., B. Plucar: Pharmacology and toxicology of absinthe. *J. Appl. Biomed.* 1, 199–205, 2003.
- Pohl L.R., R. Bales, W.F. Trager: Warfarin – stereochemical aspects of its metabolism *in vivo* in the rat. *Res. Commun. Chem. Pathol. Pharmacol.* 15: 233–256, 1976.
- Rybak L.P., C. Whitworth: Ototoxicity of indacrinone is stereospecific. *Hear Res.* 31: 169–174, 1987.
- Sanchez C., P.B. Bergqvist, L.T. Brennum, S. Gupta, S. Hogg, A. Larsen, O. Wiborg: Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. *Psychopharmacology (Berl)*. 167: 353–362, 2003.
- Schwarz U.I.: Clinical relevance of genetic polymorphisms in the human CYP2C9 gene. *Eur. J. Clin. Invest.* 33, Suppl 2: 23–30, 2003.

✉ **Address:**

Jiří Patočka, Department of Toxicology, Military Medical Academy, Hradec Králové and Faculty of Health and Social Studies, University of South Bohemia, České Budějovice, Czech Republic
