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STEREOCHEMISTRY AND ITS ROLE IN DRUG DESIGN

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ABSTRACT: When designing small molecules to interact with the targets, one should consider stereoselectivity. As considerations for exploring structure space evolve, chirality is increasingly important. Binding affinity for a chiral drug can differ for diastereomers and between enantiomers. For the virtual screening and computational design stage of drug development, this problem can be compounded by incomplete stereochemical information in structure libraries leading to a "coin toss" as to whether or not the "ideal" chiral structure is present. Creating every stereoisomer for each chiral compound in a structure library leads to an exponential increase in the number of structures resulting in potentially unmanageable file sizes and screening times. Therefore, only key chiral structures, enantiomeric pairs based on relative stereochemistry need be included, and lead to a compromise between exploration of chemical space and maintaining manageable libraries. In clinical environments, enantiomers of chiral drugs can have reduced, no, or even deleterious effects. This underscores the need to avoid mixtures of compounds and focus on chiral synthesis. Governmental regulations emphasizing the need to monitor chirality in drug development have increased. The United States Food and Drug Administration issued guidelines and policies in 1992 concerning the development of chiral compounds. These guidelines require that absolute stereochemistry be known for compounds with chiral centers and that this information should be established early in drug development so that the analysis can be considered valid. From exploration of structure space to governmental regulations it is clear that the question of chirality in drug design is of vital importance.

INTRODUCTION: Stereochemistry, a sub-discipline of chemistry, involves the study of the relative spatial arrangement of atoms within molecules. An important branch of stereochemistry is the study of chiral molecules [1]. Stereochemistry is also known as 3D chemistry because the prefix "stereo-" means "three-dimensionality [2].

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Stereochemistry is a hugely important facet of chemistry, and the study of stereochemical problems spans the entire range of organic, inorganic, biological, physical and supramolecular chemistries. Stereochemistry includes methods for determining and describing these relationships; the effect on the physical or biological properties these relationships impart upon the molecules in question and how these relationships influence the reactivity of the molecules in question (dynamic stereochemistry).

Louis Pasteur could rightly be described as the first stereo chemist, having observed in 1849 that salts of tartaric acid collected from wine production

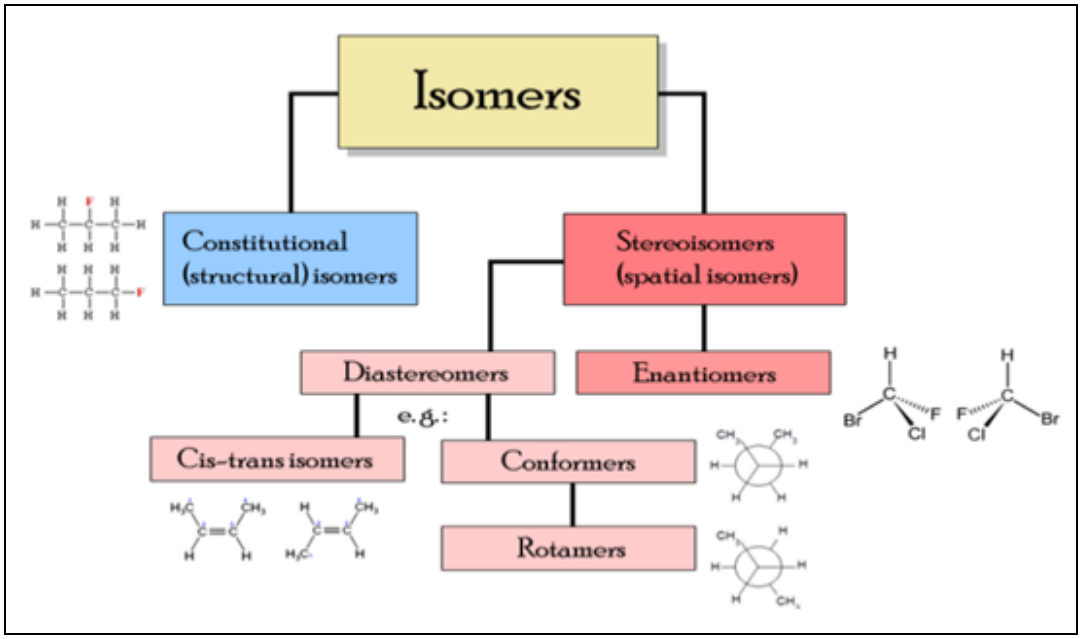
vessels could rotate plane-polarized light, but that salts from other sources did not. This property, the only physical property in which the two types of tartrate salts differed, is due to optical isomerism. In 1874, Jacobus Henricus van't Hoff and Joseph Le Bel explained optical activity in terms of the tetrahedral arrangement of the atoms bound to carbon. One of the most infamous demonstrations of the significance of stereochemistry was the thalidomide disaster. Thalidomide is a drug, first prepared in 1957 in Germany, prescribed for treating morning sickness in pregnant women. The drug, however, was discovered to cause deformation in babies. It was discovered that one optical isomer of the drug was safe while the other had teratogenic effects, causing serious genetic damage to early embryonic growth and development.

In the human body, thalidomide undergoes racemization: even if only one of the two stereoisomers is ingested, the other one is produced. Thalidomide is currently used as a treatment for leprosy and must be used with contraceptives in women to prevent pregnancy-related deformations. This disaster was a driving force behind requiring strict testing of drugs before making them available to the public [3].

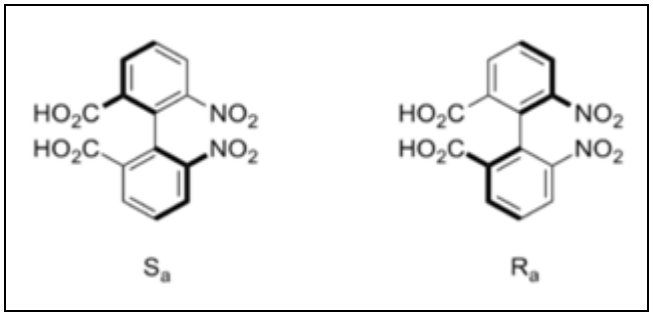
Cahn-Ingold-Prelog priority rules are part of a system for describing a molecule's stereochemistry. They rank the atoms around a stereocenter in a standard way, allowing the relative position of these atoms in the molecule to be described unambiguously. A Fischer projection is a simplified way to depict the stereochemistry around a stereocenter.

Types of stereoisomerism are:

- Atropisomerism
- *Cis-trans* isomerism
- Conformational isomerism
- Diastereomers
- Enantiomers
- Rotamers



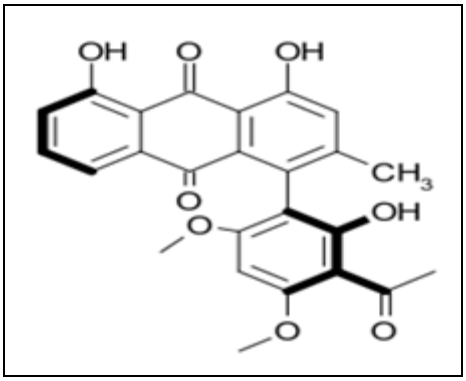
Atropisomers: Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers [4, 5]. The word atropisomer is derived from the Greek a, meaning not, and tropos, meaning turn. The name was coined by Kuhn in 1933, but atropisomerism was first detected in 6, 6'-dinitro-2, 2'-diphenic acid by Cristie in 1922.



Oki defined atropisomers as conformers that interconvert with a half-life of more than 1000 seconds at a given temperature. Atropisomers are an important class of compounds because they display axial chirality. They differ from other chiral compounds in that they can be equilibrated thermally whereas in the other forms of chirality isomerization is usually only possible chemically.

The most important class of atropisomers are biaryls such as *diphenic acid*, which is a derivative of biphenyl with a complete set of ortho substituents. Others are dimers of naphthalene derivatives such as 1, 1'-bi-2-naphthol. In a similar way, aliphatic ring systems like cyclohexanes linked through a single bond may display atropisomerism provided that bulky substituents are present.

Examples of naturally occurring atropisomers include vancomycin and knipholone, which is found in the roots of Kniphofia Foliosa of the family Asphodelaceae.

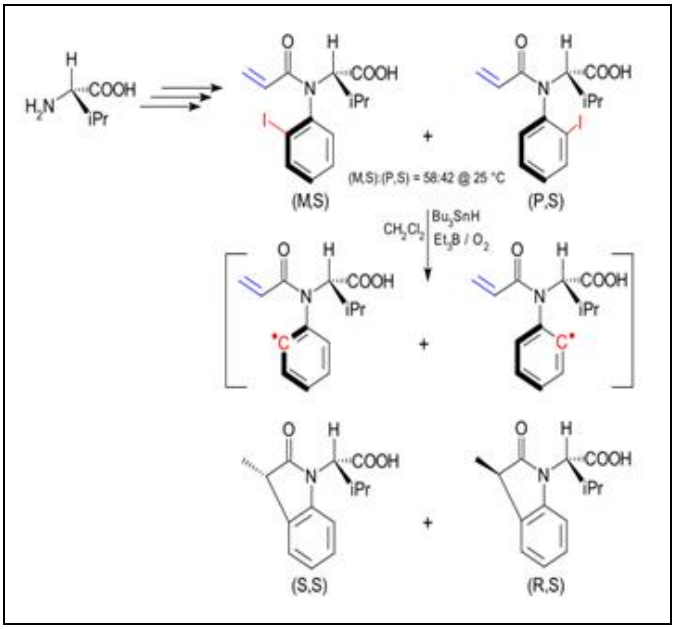


Separation of atropisomers is possibly by chiral resolution methods such as selective crystallization. In an atropo-enantioselective or atropselective synthesis one atropisomer is formed at the expense of the other. Atroposelective synthesis may be carried out by use of chiral auxiliaries like a CBS catalyst in the total synthesis of knipholone or by approaches based on thermodynamic equilibration when an isomerization reaction favors one atropisomer over the other.

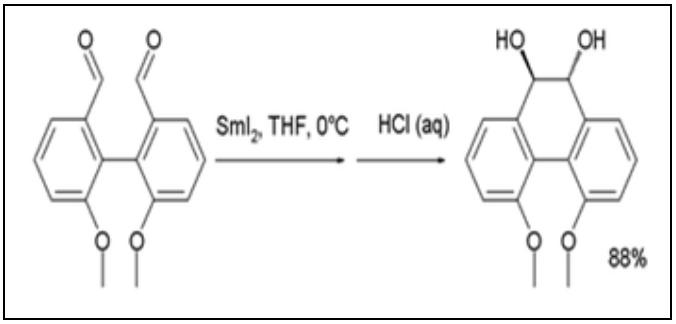
In organic chemistry BINAP is a ligand that is used in the preparation of optically active stereoisomers.

Scope: In one application the asymmetry in an atropisomer is transferred in a chemical reaction to a new stereocenter [6, 7, 8, 9, 10]. The atropisomer is an iodoaryl compound synthesized starting from (S)-valine and exists as the (M, S) isomer and the (P, S) isomer. The interconversion barrier between the two is 24.3 kcal/mol (101.7 kJ/mol). The (M, S) isomer can be obtained exclusively from this mixture by recrystallization from hexanes.

The iodine group is homolytically removed to form an aryl radical by a tributyltin hydride/ triethylboron/oxygen mixture as in the Barton-McCombie reaction. Although the hindered rotation is now removed in the aryl radical the intermolecular reaction with the alkene is so much faster than rotation of the carbon-nitrogen bond that the stereochemistry is preserved. In this way, the (M, S) isomer yields the (S, S) dihydroindolone.



An axial chirality switch is reported for a diol prepared from intramolecular pinacol coupling of the corresponding di-aldehyde with samarium (II) iodide. In methanol, this compound has the two alcohol groups in equatorial positions but in hexane helicity is reversed with both groups in axial positions.



Stereochemistry and its Role in Drug Design: [11, 12, 13, 14, 15] Approximately 25% of drugs are marketed as either racemates or mixtures of diastereoisomers. Such stereoisomers frequently differ in terms of their biological activity and pharmacokinetic profiles and the use of such mixtures may contribute to the adverse effects of the drug particularly if they are associated with the inactive or less active isomer.

In recent years drug stereochemistry has become a significant issue for both the pharmaceutical industry and the regulatory authorities. The significance of stereoisomerism in antimicrobial agents is addressed in this review using examples drawn from the β-lactams, as being representative of semisynthetic agents, and the quinolones, as examples of synthetic agents. Within these two groups of compounds, it is clear that stereochemical considerations are of significance for an understanding of concentration-effect relationships, selectivity in both action and inactivation and for an appreciation of the mode of action at a molecular level.

In the case of some agents, the use of a single isomer is precluded due to their facile epimerization, *e.g.* carbenicillin, in the case of others, there are potential advantages with the use of single isomers, *e.g.* ofloxacin [16, 17, 18]. However, in the case of latamoxef, a compound which undergoes *in-vivo* epimerization with a half-life similar to its apparent serum elimination half-life the situation is by-no-means clear cut. These agents emphasize the importance of considering each compound individually, *i.e.* on a case-by-case basis, before deciding to use a single isomer or stereoisomeric mixture.

A survey of 1675 drugs carried out in the early 1980s, indicated that 1200 (71.6%) could be classified as synthetic and 475 (28.4%) as natural products or semisynthetic agents. Four hundred and eighty (28.7%) of the synthetic compounds were chiral and of these 58 (3.5%) were marketed as single isomers; the remainder (25.2%) were marketed as racemates. In contrast 469 (28%) of the natural or semisynthetic products were chiral and of these 98.3% (461) were marketed as single isomers. More recent surveys have indicated that the position with respect to natural/ semisynthetic products has not changed greatly but that the proportion of synthetic single isomer drugs increased considerably up to 1991.

It should be obvious from the above figures that drug chirality is not a problem restricted to a single therapeutic group of agents, but an ‘across-the-board’ problem.mixtures of stereoisomers is found in the majority of therapeutic groups. As many of the agents used in antimicrobial chemotherapy are natural, or semisynthetic, the reader may wonder why this issue is being addressed in this journal.

The problems associated with drug stereochemistry are complex, many of the semisynthetic agents are marketed as mixtures of diastereoisomers and a number of the synthetic agents are used as racemates. Such mixtures are regarded by some as 'compounds containing 50% impurity' and their use is essential 'polypharmacy' with the proportions in the mixture being determined by chemical properties rather than therapeutic need. As a result of this increased concern, drug stereochemistry has become an issue for both the pharmaceutical industry and all the major regulatory authorities.

At present, there is no absolute requirement from any authority for the development of drugs as single isomers, but in the future, the introduction of mixtures will require scientific justification. Indeed, several compounds currently marketed as racemates are undergoing re-evaluation as single isomer products, and while relatively few, *e.g.* dexfenfluramine, have been remarketed to date, several such compounds are in an advanced stage of development. A compound frequently cited, particularly in the popular press, to support arguments for the development of single isomer drugs is the teratogen thalidomide. Recent investigations have indicated that the R-enantiomer of thalidomide has hypnotic properties while (S)-thalidomide is both a hypnotic and a teratogen in SWS mice. Thus, if the drug had been used as a single isomer then the tragedy of the early 1960s could have been avoided. However, some older data obtained with a more sensitive test species, New Zealand White rabbits, indicates that both enantiomers of the drug are teratogenic [19]. An additional problem with the compound is its facile racemization in biological media. Taken together these data indicate that the situation with

thalidomide is by no means as clear as some of the secondary literature implies.

In this review when the structure of a molecule is specifically referred to the name of the molecule is followed by a number in parentheses. These structures can be located within the figures using this numerical identification.

Chirality and Antimicrobial Agent: [20]

Enantiomers are stereoisomers which are non-superimposable mirror images of one another and therefore by definition are pairs of compounds related as an object to its mirror image. Such isomers are said to be chiral (Greek *chiros* meaning handed) and are referred to as optical isomers, due to their ability to rotate the plane of plane-polarized light, which is equal in magnitude but opposite in direction. The term diastereoisomers refer to all other stereoisomeric compounds, regardless of their ability to rotate plane-polarized light, and the definition, therefore, includes both optical and geometrical isomers.

The fundamental distinction between enantiomerism and diastereoisomerism is that in a pair of enantiomers the intramolecular distances between non-bonded atoms are identical, whereas in diastereoisomers they are not. Thus, the energy content of a pair of enantiomers is essentially identical and therefore their physicochemical properties, *e.g.* lipid solubility, melting points, *etc*., are also identical, and the separation, or resolution, of a racemic mixture (a 1:1 mixture of enantiomers) was, until relatively recently, fairly difficult.

Diastereoisomers differ in energy, and therefore in physicochemical properties, and maybe relatively readily separable by standard chemical techniques. In terms of compounds of interest in medicinal chemistry the most frequent cause of chirality results from the presence of a tetracoordinate carbon center in a molecule to which four different groups are attached. The presence of one such center in a molecule gives rise to a pair of enantiomers, the presence of n such centers gives rise to 2" stereoisomers and half that number of pairs of enantiomers. Those isomers which are not enantiomeric are diastereomeric. Diastereoisomers which differ in the configuration about one chiral center only are termed epimers.

As pointed out above, in physicochemical terms enantiomers differ only in the direction of rotation of the plane of plane-polarized light and this property is frequently used in their designation. Those isomers which rotate light to the right are termed dextrorotatory, indicated by a (+)-sign, while those which rotate light to the left are termed laevorotatory indicated by a (-)-sign. A racemic mixture of the two is indicated by (±) before the name of the compound. It is important to appreciate that this designation yields information concerning the physical property of the material but does not give information concerning the three-dimensional spatial arrangement, or absolute configuration, of the molecule. Some care is also required when using the direction of rotation as a stereochemical descriptor as both the magnitude and direction of the rotation may vary with the experimental conditions used to make the determination. For example, chloramphenicol contains two chiral centers and therefore four stereoisomeric forms are possible.

The active isomer has the *R, R*-absolute configuration. However, this compound is dextrorotatory when the determination is made in ethanol and laevorotatory in ethyl acetate. Additional complications arise if the drug material is a mixture of two diastereoisomers, *e.g.* latamoxef (moxalactam) consists of a mixture of two epimers both of which are laevorotatory and are designated as *(-)-(R)-* and (-)-(S)-latamoxef (moxalactam) [21].

In this case, the designation of the material by optical rotation is meaningless and provides no information concerning the stereochemical composition of the material, *i.e.* single isomer or mixture. Once the structure of a stereoisomer has been determined by, for example, X-ray crystallography then the configuration of the molecule may be indicated by the use of a prefix letter to the name of the compound. Two systems are frequently used, the *R/S* Cahn-Ingold-Prelog system, or the older D/L system. The D/L system relates the absolute stereochemistry of a molecule to that of the enantiomers of either the carbohydrate D-glyceraldehyde or the amino acid L-serine. The use of this system has to lead to ambiguities and is now usually restricted in use to carbohydrates and amino acids.

In the *R/S* system once the structure of the molecule has been determined the substituent atoms attached to the chiral center are ranked in order of priority based upon their atomic numbers. The higher the atomic number the greater the priority. The molecule is then viewed from the side of the molecule opposite the group of lowest priority and if the remaining highest to lowest priority atoms are in a clockwise direction, *i.e.* to the right, the chiral center is of the rectus or R-absolute configuration and if to the left the isomer is of the sinister or S-absolute configuration.

A particular problem in the nomenclature and stereochemical designation of semisynthetic compounds occurs as both the above systems may be used to define the structure of a single molecule. For example, the absolute stereochemistry of the 6-aminopenicillanic acid and 7-aminocephalo-sporanic acid nuclei have been determined and defined using the *R/S* system but the addition of a side chain, *e.g.* Ampicillin, Cephalexin may result in the introduction of an additional chiral center, which in the case of these two compounds is frequently defined in terms of the D/L system.

Thus, the British Pharmacopoeia (1993) defines Ampicillin as 6R-6-(α-D-phenylglycylamino) penicillanic acid. The side-chain chiral center being denoted by the D/L system and only in the case of Ampicillin is the stereochemistry of the ring system indicated and then for only one of the three centers. Within the literature, the two possible diastereoisomers arising from the introduction of the side chain in these two compounds are frequently referred to in terms of D and L.

Chirality and Biological Activity: As pointed out above differences between enantiomers are under normal circumstances difficult to detect. However, when placed in a chiral environment these differences become much more marked. Biological systems, at a molecular level, are intensely chiral environments being composed, in mammals at least, of macromolecules, *e.g.* proteins, glycolipids, and polynucleotides, from the chiral building blocks of L-amino acids and D-carbohydrates. As many of the processes of drug action and disposition involve an interaction between the enantiomers of a drug molecule and a chiral biological macromolecule it is hardly surprising that stereoselectivity, or specificity, is observed in biological systems. The interaction between a drug molecule and a receptor surface or enzyme active site is associated with bonding interactions between the functionalities of the drug and complementary sites on the receptor surface. Such interactions may have considerable steric constraints, for example in terms of interatomic distance and steric bulk, between such functionalities.

In the case of stereoisomers, the three-dimensional spatial arrangement of the groups is also of considerable significance. This situation is illustrated with respect to a pair of enantiomers. In the case of the 'active' enantiomer three simultaneous bonding interactions between the drug and the biological surface take place, whereas the 'inactive' isomer may take part in two such interactions. Thus the 'fit' of the two enantiomers to the receptor surface are different and the binding energies of the interaction also differ.

The differential pharmacological activity of drug enantiomers has also given rise to additional terminology. Thus the isomer with the higher receptor affinity, or activity, is termed the eutomer, and that with the lower affinity, or activity, the distomer. The ratio of activities, a measure of the stereoselectivity, is termed the Eudismic Ratio. The above designations and the Eudismic Ratio refer to one biological action only, and for a dual-action drug, the eutomer for one activity may be the distomer for the other.

Examples are known in which the differential biological properties of a pair of enantiomers results in the marketing of both isomers with different therapeutic indications. Both enantiomers of the drug propoxyphene are available, one as the analgesic dextropropoxyphene, with the *(2R*, 3S)-configuration, and the other laevopropoxyphene ((2S, 3R)-configuration) as an antitussive.

In the case of this example not only are the molecules mirror image related but so are their trade names (Darvon/Novrad). Stereoselectivity is also observed in drug disposition particularly for those processes which depend on an interaction with a chiral biological macromolecule, *e.g.* active transport processes, binding to plasma proteins, and drug metabolism [22].

The passage of the majority of drugs through biological membranes depends on their physicochemical properties, *e.g.* lipid solubility, pKa, size. In such cases, differences between enantiomers would not be expected, but differences between diastereoisomers may well occur as a result of differences in their solubility. For example, the water solubility of the D-diastereoisomer of ampicillin is greater than that of the L-diastereoisomer.

However, if a chiral drug molecule is a substrate for an active transport process, then differences between both enantiomers and diastereoisomers would be expected with preferential absorption of the stereoisomer with a spatial arrangement similar to that of the natural substrate.

In theory, such processes may be expected to increase the rate rather than the extent of absorption. The bioavailability of D-Methotrexate is only 2.5% that of the L-isomer. Similarly, selective transport processes may influence drug distribution by selective tissue uptake and renal excretion, as a result of active secretion and/or reabsorption. Plasma protein binding may also influence drug stereoisomer distribution and renal excretion.

In metabolism, a process resulting from a direct interaction between a drug and a chiral macromolecule, stereo differentiation is the rule rather than the exception and stereoselective metabolism is probably responsible for the majority of the differences observed in enantioselective drug disposition [22, 23.]

As a result of the above processes, the pharmacokinetic profiles of the enantiomers of a drug administered as a racemate may differ markedly. Pharmacokinetic parameters, *e.g.* clearance, the volume of distribution, half-life, *etc*., based on the determination of 'total' drug substance present in biological samples is essentially meaningless data and potentially highly misleading or "sophisticated nonsense".

As pointed out above many of the agents used in antimicrobial chemotherapy are natural or semisynthetic products and frequently single isomers are used. However, mixtures of diastereoisomers and enantiomers do occur and the remainder of this article will examine such cases using the β-lactams and quinolone derivatives as representative examples.

Ofloxacin: The stereoselectivity of the *in-vitro* antimicrobial action of the enantiomers of ofloxacin has been referred to above. The S-enantiomer being between 8- to 128-fold more active against both Gram-positive and Gram-negative bacteria than the R-antipode [16].

The target enzyme of the quinolone derivatives is believed to be DNA gyrase (bacterial topoisomerase II) and a good correlation between antimicrobial activity, as determined by MIC concentrations and IC_{50} concentrations for inhibition of DNA gyrase have been obtained for the quinolones. In the case of ofloxacin, the (—)-S-enantiomer is 9.3 and 1.3 times more active than the (+)-R-enantiomer and the racemate in terms of enzyme inhibition. The rank order of potencies is identical to that observed for MIC activity. As there are similarities between DNA gyrase and mammalian topoisomerase II it is of interest to examine the activity of the quinolones on topoisomerase II and hence their effects on mammalian cells.

In the case of ofloxacin the rank order of potency against topoisomerase II, obtained from fetal calf thymus, is the same as that for DNA gyrase inhibition, i.e. *S* > *R*,*S* > *R*. However, the relative activity *(R/S)* of the two enantiomers decreases from 12.4 with DNA gyrase to 1.8 against topoisomerase II, but more importantly, (—)-S-ofloxacin is about 6.7 fold more selective than the R-enantiomer (19b). It is also of interest to note that the non chiral analog (structure 19, R' = R2 = H) is the least selective compound of the four (Table). Thus, the presence and orientation of the methyl group at the chiral center not only determines the potency of the compound but also increases the selectivity.

The interaction between the quinolones and both DNA gyrase and DNA has been the subject of extensive investigation. Based on these investigations Shen and coworkers have proposed a cooperative quinolone-DNA binding model for the inhibition of DNA gyrase. The proposed model requires self-association of the drug molecules *via*

both *n-n* stacking interactions between the bicyclic ring systems, together with hydrophobic interactions involving the substituents on the ring nitrogen.

The final complex has been depicted as involving at least four drug molecules such that the hydrophilic groups are projected 'outside' the complex, the 'core' being hydrophobic.

In terms of substituents on the quinolone nucleus, hydrophobic groups are required at Nl, to enhance interactions between individual molecules, and the steric bulk of substituents at C7 does not appear to be a critical feature for useful activity. This latter point agrees with the observations presented above regarding the lack of significant differences between the activity of enantiomers on the introduction of a center of chirality in the 7-position substituent With the use of molecular graphics techniques have attempted to rationalize the differential activity of the enantiomers of ofloxacin in terms of their interaction model.

The oxazine fused ring in ofloxacin is partially saturated and is therefore nonplanar with a degree of conformational flexibility. Such conformational flexibility will also influence the orientation of the methyl group at the chiral center to the ring, which may take up either equatorial or axial positions, and thus influence the structure of the complex formed by molecular self-association. The data obtained by molecular modeling indicated that the most stable molecular complexes for the two enantiomers were also mirrored images of one another and that the enantiomers cannot stack in the same way to the asymmetric DNA binding site. Sato *et al.,* (1990) have reported that the specific binding of both enantiomers of ofloxacin to supercoiled DNA is essentially the same, between 5 and 6 M, but that the apparent number of bound drug molecules varied with configuration, being four and two for (S)- and (R)-ofloxacin, respectively. In terms of the model proposed by Shen *et al.,* (1990) this difference may be due to an unfavorable binding orientation of the R-enantiomer such that the molecular self-association cannot take place.

The metabolism and pharmacokinetics of the enantiomers of ofloxacin have been investigated following their administration as such and as both racemic and non-racemic mixtures, to the rat, dog, and cynomolgus monkey. Following their individual administration to rats, the serum concentrations of (R)-ofloxacin were significantly higher than those of the S-enantiomer with a corresponding greater area under the serum concentration-time curve (AUC) and a longer apparent serum elimination half-life.

These pharmacokinetic differences arise due to stereoselective conjugation of (S')-ofloxacin with glucuronic acid, together with preferential biliary excretion of (S-ofloxacin, and its glucuronide, and urinary excretion of (R)-ofloxacin.

In addition, *in-vitro* studies, using rat hepatic microsomal preparations have indicated relatively minor differences in the apparent *Km* for glucuronide formation of the two enantiomers (1.43 and 1.14 mM for *(R)* - and (S)-ofloxacin, respectively) but a 6.5-fold difference in *V^\,* the ratio of *VmMx/Km,* an index of intrinsic hepatic clearance, *S/R* is 8.1.

Further studies indicated that the R-enantiomer is a competitive inhibitor of the glucuronidation of (S')-ofloxacin with a A", the value of 2.92 mM. As a result of this enantiomeric interaction in metabolism the serum concentrations of (S-ofloxacin are markedly increased following administration of the racemic drug compared with those observed following an equivalent dose of the single enantiomer, resulting in a 1.7-fold increase in the AUC. Following administration of racemic ofloxacin to cynomolgus monkeys significant differences were observed between the two enantiomers in AUC *(S > R),* mean residence time (5 > *R)* and total clearance *(R > S).*

Interestingly, administration of the 5-enantiomer with increasing amounts of the/?-isomer resulted in an increase in AUC, a decrease in the volume of distribution and a decrease in both total and renal clearance of (S)-ofloxacin. As the drug undergoes minimal metabolism in this species these differences cannot be rationalized by metabolic interactions. The renal excretion of ofloxacin is believed to involve both glomerular filtration and tubular secretion, mediated by the organic cation transport system.

Thus the enantiomer-enantiomer interaction in the case of the monkey may be explained by Competition for the secretion or reabsorption process. In contrast to the above two species, no differences were observed in the pharmacokinetic parameters of the two enantiomers in the dog.

The dispositional properties of the enantiomers of ofloxacin illustrate the potential problems which may arise when dealing with racemic mixtures, *i.e.* stereoselectivity in metabolism resulting in stereoselectivity in routes of excretion; enantiomeric interactions in both metabolism and active transport processes; species variability in enantiomeric metabolism and excretion together with the associated difficulty of species selection for toxicological evaluation.

Following the oral administration of racemic ofloxacin to healthy volunteers, the serum concentration-time profiles of the individual enantiomers are similar to those obtained following the determination of total drug concentrations. Small, but statistically significant, differences were observed between the enantiomers in AUC *(S > R),* mean residence time *(S > R)* and both total and renal clearance *(R > S)* but not in plasma protein binding or volume of distribution.

As the drug undergoes minimal metabolism in man the differences in the pharmacokinetic profiles of the two enantiomers may be accounted for by stereoselectivity [24, 25] in renal clearance. If a similar situation with respect to the reduced renal clearance of (S')-ofloxacin in the presence of the R-enantiomer observed in the monkey occurs in man, it could be argued that it may be advantageous to administer the racemate rather than the single active enantiomer and thus increase the serum concentrations of the active isomer. However, it is of interest to note that the single active S-enantiomer of ofloxacin, levofloxacin, has been recently marketed in Japan and is currently undergoing Phase III clinical trials in Europe and the USA.

Concluding Comments: The above discussion has attempted to highlight the significance of stereochemical [26]. Considerations in the area of antimicrobial agents. In the current regulatory climate, all the components present in a medicinal product require justification, and as has been observed in other therapeutic areas, the introduction of single stereoisomers of both new and existing chiral drugs is likely to increase (the so-called racemic switches).

However, such introductions are not without problems and may provide unexpected results. Labetalol, an established combined a- and j3-blocking drug used in the treatment of cardiovascular disease, contains two chiral centers and the marketed material is a mixture of all four stereoisomeric forms. Of these stereoisomers, the blocking activity resides in the *R,R-isomer,* the a-blocking activity in the S,-isomer and the remaining pair are essentially inactive. Clinical trials with the single blocking, *R, R-\somtr,* named dilevalol, resulted in elevated liver function tests in a small number of patients.

This toxicity had not been observed with labetalol and resulted in the withdrawal of the single isomer. Why such toxicity is not observed with the isomeric mixture is not clear, but this example does illustrate that removal of the isomeric 'impurity' may not be a trivial matter.

The decision to market a racemate, nonracemic isomeric mixture or single stereoisomer depends on a number of factors, including technical feasibility, *i.e.,* production on an industrial scale, stereochemical stability, toxicological profile and the clinical significance of the agent, *i.e.* the risk-benefit ratio. There are no simple answers to the single stereoisomer versus isomeric mixture debate and each example must be examined on a case-by-case basis. Several of the compounds cited above indicate the potential problems that may arise during drug development.

For example, the epimerization of carbenicillin appears to be so rapid as to preclude the use of a single isomer. Whereas, in the case of latamoxef, a compound with a half-life of epimerization under physiological conditions only slightly shorter than the apparent serum elimination half-life, the single isomer or mixture question is more difficult to answer. In the case of the quinolones, particularly with respect to ofloxacin and its derivatives, there can be little doubt of the significance of stereochemical considerations, particularly in terms

of providing an insight into the mechanism of action at a molecular level, potency, and selectivity.

Prodrugs: [22] Esterification of the carboxyl group, to yield lipophilic ester prodrugs, has been used extensively within the β-lactams in order to improve their absorption following oral administration. A number of these derivatives involve the formation of either an acyloxymethyl or acyloxyethyl function which undergoes rapid enzymatic hydrolysis *in-vivo* to yield the corresponding hydroxymethyl or hydroxyethyl esters which, being hemiacetal derivatives, spontaneously cleave with the liberation of the active β-lactam and the corresponding aldehyde.

The introduction of the hydroxyethyl function into the promoiety results in the introduction of an additional chiral center into the molecule and therefore the possibility of a pair of diastereoisomeric compounds, *e.g.* for Cefuroxime axetil and Cefdaloxime pentexil. As pointed out above diastereoisomers may differ in their physicochemical properties, *e.g.* solubility, and also in their susceptibility with respect to *in-vivo* enzymatic hydrolysis. Cefuroxime axetil is the 1-acetoxyethyl ester prodrug of cefuroxime and undergoes hydrolysis *in-vivo* to yield Cefuroxime, acetaldehyde and acetic acid. The drug material consists of an equal-parts mixture of the two possible diastereoisomers of the *1'S, 6R, 7R* and *1'R, 6R, 7R* absolute configurations. Following administration, to man the prodrug undergoes rapid hydrolysis and cannot be detected in the systemic circulation and shows a bioavailability with respect to cefuroxime of between 30 to 50% in the fasted and fed states.

Similar values for bioavailability have been reported following administration of the prodrug to the rat and may be due to an esterase, isolated from intestinal washings, which converts the ester to the unabsorbed drug (Campbell, Chantrell & Eastmond, 1987. The possible contribution of stereoselectivity in the intestinal enzymatic hydrolysis of the prodrug in man is not known, but such selectivity may contribute to the observed bioavailability of between 30-50%. In human blood the mixture of diastereoisomers has a half-life of 3.5 min, *i.e.* is rapid, and thus stereoselectivity in hydrolysis is not a problem.

Differential chemical hydrolysis and photochemical stability of cefuroxime axetil diastereoisomers have also been observed. However, the absolute configurations of the two compounds were not reported.

Cefdaloxime is a third-generation cephalosponn with high antibacterial activity against both Gram-positive and Gram-negative pathogens. The drug is poorly absorbed from the gastrointestinal tract and has been esterified to yield the pivaloyloxyethyl prodrug. Similarly to cefuroxime axetil the formation of the prodrug results in the introduction of an additional chiral center and two diastereoisomers of absolute configurations l'S, *6R, 1R* for HR 916 K (16a) and *VR, 6R, 1R* for HR 916 J (16b).

Examination of the *in-vivo* activity of the diastereoisomers, following their individual and mixed administration, in a mouse protection assay indicated similar activity profiles for all three stereoisomeric forms of the prodrug. A more extensive pharmacokinetic study in mice, rats, and dogs, however, yielded some species differences. In the mouse all three forms of the prodrug showed rapid and essentially complete absorption; in the rat bioavailability of the drug was reduced but no differences were observed between the individual diastereoisomers. However, in the dog the 1S, 6R, 7R-diastereoisomer (HR 916 K;) showed approximately three times the bioavailability of the 1r,6R,7R-diastereoisomer (HR 916 J;) as determined by comparison of the areas under the cefdaloxime serum concentration-time curves and urinary drug recovery.

Defossa *et al.*, (1992) have also stated that the absorption of the l'S, 6R, and 7R-diastereoisomer was significantly higher in man, but no experimental data were presented. This diastereoisomer, HR 916 K, has been selected for evaluation and the pharmacokinetic properties of cefdaloxime following administration of the prodrug to man have been reported.

Stereoselectivity in the absorption of diastereoisomeric prodrugs, together with the subsequent availability of the drug, may arise as a result of differential solubility at the absorption site, rates of diffusion through the gut wall and

enzymatic activity in the gut contents, mucosa, liver and blood, and as such the potential problems associated with the introduction of a chiral promoiety into a molecule need to be taken into consideration at the compound design stage.

Stereochemical Terminology and Pharmacodynamic Activity: [27, 28, 29] The differential pharmacodynamic activity of drug stereoisomers has resulted in additional terminology. The enantiomer with the greater affinity, or activity, is termed the eutomer, whereas that with the lower affinity or activity is the distomer.

The ratio of affinities, or activities, eutomer to **Fig. 5** Four-point location model. If the target/binding site(s) protrude from a surface or are in a cleft in the macromolecular structure, then either enantiomer may bind at three sites (*e.g.*, B_ _ _ _B0, C_ _ _ _C0 and D_ _ _ _D0), and the bonding interaction is determined by the approach direction. Alternatively, a fourth interaction/location may be required (*i.e.*, A_ _ _ _A0 or A_ _ _ _A00). The initial interaction may result in conformational changes in structure as proposed in the conformationally driven model. Distomer is known as the eudismic ratio and its logarithm as the eudismic index. The slope of a plot of eudismic index versus the logarithm of the affinity of the eutomer (ideally expressed as either pA2 or pD2 values in pharmacology or ki and km values in enzymology) for a homologous or congenic series is known as the eudismic affinity quotient (EAQ).

The EAQ is a quantitative measure of the stereoselectivity within a compound series for a particular biological effect. A positive slope is indicative of Pfeiffer's rule, *i.e.*, the greater the difference in pharmacological activity between a pair of enantiomers, the greater the specificity exhibited by the eutomer.

The original hypothesis is based on a plot of isomeric activity ratio versus the average human dose for a diverse series of drugs. In hindsight, the linear relationship obtained is somewhat surprising, as no considerations were made for differences in enantiomeric disposition, receptor type, or drug action, *i.e.*, agonist or antagonist. A number of subsequent investigations have provided supporting data for this hypothesis, though exceptions to the rule have also been observed.

In addition to a reversal in potency, a dual-action drug may show equipotency for one activity. Carvedilol is a nonselective b-adrenoceptor antagonist with vasodilator activity used in the treatment of hypertension and angina. (S)-Carvedilol is a potent competitive inhibitor at b1-adrenoceptors, whereas the R-enantiomer is considerably less potent, with pA2 values of 9.4 and 3.9 for (S) - and (R)-carvedilol, respectively. In contrast, the enantiomers are essentially equipotent with respect to a1-adrenoceptor blockade, with pA2 values of 7.87 and 7.79 for the S- and R-enantiomers, respectively.

Thus the vasodilator and antihypertensive effects of the drug arise as a result of the a1-adrenoceptor blockade of both enantiomers and the b1-blockade from the S-enantiomer which prevents reflex tachycardia. Similarly to amosulalol, outlined above, the lack of stereoselectivity with respect to a1-adrenoceptor blockade is presumably associated with the hydroxy group being located in a noncritical region of the molecule for receptor interaction.

Pharmacodynamic Complexities: [30] The most important differences between enantiomers occur in drug-receptor interactions. Indeed, Lehmann [34] has stated, ''the stereoselectivity displayed by pharmacological systems constitutes the best evidence that receptors exist and that they incorporate concrete molecular entities as integral components of their active-sites.'' In contrast to the pharmacokinetic properties of a pair of enantiomers, differences in pharmacodynamic activity tend to be more marked, and eudismic ratios of 100 to 1000 are not uncommon.

Examination of the pharmacodynamic properties of a pair of enantiomers may yield a number of possible scenarios: The required activity resides in a single stereoisomer, the enantiomer being biologically inert. Both enantiomers have similar pharmacodynamic profiles. The pharmacodynamic activity of a pair of enantiomers differs so that both may be marketed with different therapeutic indications. The enantiomers may have opposite effects at the same biological targets.

One stereoisomer may antagonize the adverse effects of its enantiomer. The required activity resides in both stereoisomers, but the adverse effects are predominantly associated with one enantiomer. The adverse effects are associated with both enantiomers, but the required effect is predominantly associated with one enantiomer. There are relatively few examples of drugs in which the pharmacodynamic activity is restricted to a single stereoisomer, the enantiomer being totally devoid of activity. One such example is a-methyldopa; the antihypertensive activity resides solely in the S-enantiomer and this agent is marketed as a single isomer.

The angiotensin-converting enzyme (ACE) inhibitor imidapril is another example: the inactive enantiomer is essentially devoid of activity, being greater than a million-fold less active than the eutomer similarly, there are few examples where the required beneficial activity resides in a single stereoisomer and the adverse effects, or toxicity, reside in its enantiomer. Instances are also known where the activity of a pair of enantiomers differ sufficiently that both are marketed with different therapeutic indications, *e.g.*, dextromethorphan and levomethorphan, and levopropoxyphene and dextropropoxyphene.

In the case of both these pairs of compounds, the first named is marketed as an antitussive whereas their enantiomers are analgesics. That a pair of enantiomers can have opposite actions at the same receptor was at one time considered to be extremely rare. However, in recent years this phenomenon has become somewhat more common, which is presumably associated with the increased awareness of the potential significance of stereoselectivity in drug action. Whatever the reason, it is obvious that the evaluation of the activity of a racemate does not provide a clear indication of the properties of the drug.

The analgesic agent racemic picenadol is a partial m-receptor agonist that arises as a result of the greater agonist potency of the (þ) - 3S, 4R-stereoisomer than the weaker antagonist activity of (_)-picenadol at the same receptor. Similarly, (R)-sopromidine is an H2-agonist, whereas its S-enantiomer is an antagonist, the racemate being a partial agonist on guinea-pig atrium preparations. A number of aporphine derivatives have also been shown to elicit opposite effects at the same receptor. For example, (R)-11-hydroxy-10-methylaporphine has been shown to be a selective 5-HT1A agonist, whereas its enantiomer is an antagonist (þ)-(S) apomorphine is an antagonist at D-1 and D-2 dopaminergic receptors, whereas the R-enantiomer is an agonist, and (R)-11-hydroxyaporphine activates dopamine receptors, whereas the S-enantiomer is an antagonist.

A more complex situation, illustrating that resolution and evaluation of the pharmacodynamic properties of the individual enantiomers present in a racemate may provide considerable insight into the observed activity of the racemate, is provided by an examination of 3-(3-hydroxyphenyl)-N-npropylpiperidine and its analogs. The initial evaluation of the drug was carried out on the racemate, which was described as a highly selective agonist at dopaminergic autoreceptors. Following resolution, the R-enantiomer was found to selectively stimulate presynaptic dopaminergic receptors at high doses and postsynaptic receptors at lower doses.

In contrast, the S-enantiomer stimulated presynaptic dopamine receptors and blocked postsynaptic receptors. Thus following the racemate, the postsynaptic stimulation of the R-enantiomer is counteracted by the blockade due to the S-enantiomer resulting in a selective profile for the racemate.

Stereo Selectivity in Pharmacokinetics: [31, 32] Differentiation between stereoisomers also occurs in drug disposition and is of particular significance for those processes that depend upon a direct interaction between the drug and a chiral biological macromolecule, *e.g.*, active transport processes, binding to plasma and tissue proteins, and drug metabolism.

Absorption: The absorption and transport of the majority of drugs across biological membranes occur by passive diffusion, a process dependent upon physicochemical properties, *i.e.*, lipophilicity, ionization, and molecular size. Since enantiomers have identical physicochemical properties, stereoselectivity would not be expected; even though membrane phospholipids are chiral, the

significance of lipophilicity appears to outweigh that of compound chirality.

In contrast, differences between diastereoisomers may occur as a result of their differential solubility. However, in the case of compounds transported *via* carrier-mediated mechanisms, *e.g.*, facilitated diffusion or active transport, processes involving direct interaction between a Substrate and a carrier macromolecule, stereoselectivity is expected. Preferential absorption of the L- compared to the D-enantiomers of dopa and methotrexate have been reported.

In the case of the above examples, enantioselectivity in absorption is observed, whereas, in the case of cephalexin, a cephalosporin antibiotic, diastereoselectivity for the L-epimer occurs. The L-epimer has shown a greater affinity than and acted as a competitive inhibitor of D-cephalexin transport. The L-epimer is also more susceptible to enzyme-mediated hydrolysis, with the result that it cannot be detected in plasma.

There is currently great interest in P-glycoprotein-mediated efflux mechanisms, and such transport systems are potentially stereoselective. However, there is limited data in the literature concerning this possibility, and some reports have been the subject of controversy.

For example, *in-vitro* data suggested that the S-enantiomer of the b-adrenoceptor antagonist, talinolol, is a slightly better substrate than (R)-talinolol for P-glycoprotein, which the authors suggested accounted for the lower plasma concentrations of the S- than the R-enantiomer in vivo studies. However, a recent article suggests that modest presystemic metabolism *via* CYP 3A4, rather than P-glycoprotein efflux, is responsible for the minor but significant differences in (R) – and (S)-talinolol pharmacokinetics after oral administration.

Distribution: Stereoselectivity in drug distribution may occur as a result of binding to either plasma or tissue proteins or transport *via* specific tissue uptake and storage mechanisms. Differences between enantiomers in plasma protein binding have been reported for a number of drugs, examples of which are summarized in. Additional data for selected groups of drugs are presented in and. Similarly to other pharmacokinetic parameters, the magnitude of the differences tends to be relatively modest and maybe less than 1%.

The majority of drugs bind in a reversible manner to plasma proteins, notably to human serum albumin (HSA) and/or a1-acid glycoprotein (AGP). Acidic drugs bind preferentially to HSA, with binding at site II (benzodiazepine site) on the protein generally displaying greater enantiomeric differences than at site I (warfarin site), and basic drugs predominantly bind to AGP. It is noteworthy that stereoselectivity in binding may vary for different proteins, e.g., the protein binding of propranolol to AGP is stereoselective for the S-enantiomer, whereas binding to HSA favors (R)-propranolol. In whole plasma, the binding to AGP is dominant so that the free fraction of the R-enantiomer is greater than that of (S)-propranolol.

Enantioselective tissue uptake, which is in part a consequence of enantioselective plasma protein binding, has been reported.

For example, the transport of ibuprofen into both synovial and blister fluids is preferential for the S-enantiomer owing to the higher free fraction of this enantiomer in plasma. In addition, the affinity of stereoisomers for binding sites in specific tissues may also differ and contribute to stereoselective tissue binding, *e.g*., (S)-leucovorin accumulates in tumor cells *in-vitro* to a greater degree than the R-enantiomer. The uptake of ibuprofen into lipids is stereoselective in favor of the R-enantiomer, but this is a result of the stereospecific formation of the acyl-CoA thioester followed by incorporation as hybrid triglycerides

Metabolism: [33, 34, 35] In drug metabolism, stereo differentiation is the rule rather than the exception, and stereoselectivity in metabolism is probably responsible for the majority of the differences observed in enantioselective drug disposition. Stereoselectivity in metabolism may arise from differences in the binding of enantiomeric substrates to the enzyme active site and/or be associated with catalysis owing to differential reactivity and orientation of the target groups to the catalytic site. As a result, a pair of enantiomers is frequently metabolized at different rates and/or *via* different routes to yield alternative products.

The stereoselectivity of the reactions of drug metabolism may be classified into three groups in terms of their selectivity with respect to the substrate, the product, or both.

Thus there may be substrate selectivity when one enantiomer is metabolized more rapidly than the other; product stereoselectivity, in which one particular stereoisomer of a metabolite is produced preferentially; or a combination of the above, *i.e.*, substrate– product stereoselectivity, where one enantiomer is preferentially metabolized to yield a particular diastereoisomeric product. An alternative classification involves the stereochemical consequences of the transformation reaction. Using this approach, metabolic pathways may be divided into five groups.

- Prochiral to chiral transformations: metabolism taking place either at a prochiral center or on an enantiotopic group within the molecule. For example, the prochiral sulfide cimetidine undergoes sulphoxidation to yield the corresponding sulphoxide, the enantiomeric composition.

- Chiral to chiral transformations: the individual enantiomers of a drug undergo metabolism at a site remote from the center of chirality with no configurational consequences. For example, (S)-warfarin undergoes aromatic oxidation mediated by CYP 2C9 in the 7- and 6-positions to yield (S)-7-hydroxy- and (S)-6-hydroxywarfarin in the ratio 3.5: 1.

- Chiral to diastereoisomer transformations: a second chiral center is introduced into the drug either by reaction at a prochiral center or via conjugation with a chiral conjugating agent. Examples include the side-chain aliphatic oxidation of pentobarbitone and the keto-reduction of warfarin to yield the corresponding diastereoisomeric alcohol derivatives or the stereoselective glucuronidation of oxazepam.

- Chiral to achiral transformations: the substrate undergoes metabolism at the center of chirality, resulting in a loss of asymmetry. Examples include the aromatization of the dihydropyridine calcium channel blocking agents, *e.g.*, Nilvadipine, to yield the corresponding pyridine derivative and the oxidation of the benzimidazole proton pump inhibitors, *e.g.*, Omperazole, which undergoes CYP 3A4–mediated oxidation at the chiral sulphoxide to yield the corresponding sulphone. In the case of omeprazole, the reaction shows tenfold selectivity for the S-enantiomer in terms of intrinsic clearance.

- Chiral inversion: one stereoisomer is metabolically converted into its enantiomer with no other alteration in structure. The best-known examples of agents undergoing this type of transformation are the 2-arylpropionic acid (2-APAs) nonsteroidal anti-inflammatory drugs (NSAIDs), *e.g.*, ibuprofen, fenoprofen, flurbiprofen, ketoprofen, and the related 2-aryloxypropionic acid herbicides, *e.g.*, haloxyfop.

In the case of the 2-APAs, the reaction is essentially stereospecific, the less active, or inactive, R-enantiomers undergoing inversion to the active S-enantiomers. With the 2 aryloxypropionic acid derivatives, the transformation is in the S- to R- direction as a result of the configurational designation according to the Cahn–Ingold–Prelog sequence rules, *i.e.*, in terms of their three-dimensional spatial arrangement, the R-enantiomers of the 2-APAs correspond to the S-enantiomers of the 2-aryloxypropionic acids.

Renal Excretion: Stereoselectivity in renal clearance may arise as a result of either selectivity in protein binding, influencing glomerular filtration and passive reabsorption, or active secretion or reabsorption. Enantio selectivity in renal clearance has been reported for a number of drugs, and in the majority of instances the selectivity is relatively modest, with enantiomeric ratios between 1.0 and 3.0. In the case of the diastereoisomers quinine and quinidine, the difference is about fourfold, with values of 24.7 and 99 $mLmin^{-1}$ in man, respectively.

However, for those agents that undergo active tubular secretion, interactions between enantiomers may occur such that their excretion differs following administration as single enantiomers versus the racemate. Administration of the quinolone antimicrobial agent (S)-ofloxacin with

increasing amounts of the R-enantiomer to the cynomolgus monkey results in a reduction in both the total and the renal clearance of the S-enantiomer.

The renal excretion of ofloxacin involves both glomerular filtration and tubular secretion mediated by the organic cation transport system, and the enantiomeric interaction may be explained by competitive inhibition of the transport mechanism. Similarly, enantiomeric interactions in renal tubular secretion have been suggested to account for differences in the total and the renal clearance of the enantiomers of the uricosuric diuretic 5-dimethylsulphamoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid (DBCA).

Administration of the racemic drug to the monkey results in a 25% reduction in the total and the renal clearance, and a 30% reduction in the tubular secretion clearance, of the S-enantiomer in comparison to the values obtained following administration of the single enantiomer. In contrast, the corresponding reductions in the same parameters for (R)-DBCA did not achieve statistical significance. Coadministration of the racemic drug with probenecid resulted in significant reductions in the tubular secretion of both enantiomers but was stereoselective for (S)-DBCA, the decrease in a clearance being 53% and 14% for the S- and R-enantiomers, respectively.

Stereoselectivity in the renal clearance of the enantiomers of pindolol in man was initially reported by Hsyu and Giacomini, the tubular secretion of the S-enantiomer being 30% greater than that of (R) - pindolol. This observation has been confirmed by Somogyi *et al*., who also showed that both the renal and the tubular secretion clearance of both enantiomers is inhibited by cimetidine, presumably by inhibition of the renal organic cation transport system.

Interestingly, the renal clearance of (S) - pindolol, the enantiomer with the greater renal and the tubular secretion clearance, was reduced to a smaller extent (26%) than that of the R-enantiomer (34%), which may indicate that the secretion of the drug is mediated by more than one transporter, and that cimetidine has differential inhibitory properties.

CONCLUDING COMMENTS: There can be little doubt that stereochemical considerations in pharmacology will continue, if only because of the scientific nonsense of evaluating the properties of two agents at the same time, and such investigations will continue to provide additional insights into drug action. For a large number of agents currently available as racemates, relatively little is known concerning the biological properties of the individual enantiomers. In terms of future drug development, single stereoisomers will be the norm, and racemates will require scientific justification. ‘‘Old’’ racemates will continue to be reevaluated and reintroduced as single-enantiomer products with cleaner pharmacological profiles and, in some instances, new indications resulting in therapeutic benefits.

The move of pharmacology from being a science of ‘‘limited dimensionality’’ to one of spatial awareness has at times provoked considerable argument; indeed in some instances, the shock to the system appears to have been as traumatic as the revelation of a three-dimensional universe to the two-dimensional character in the novel mentioned in the introduction. However, if dimensional considerations result in improved drug safety and efficacy, then the double trouble involved will have been worthwhile.

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