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Stereochemistry: A Source of Problems in Medicinal Chemistry

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INTRODUCTION

Symmetry is a common aspect of nature at first view. On a molecular level, however, asymmetry dominates, both in the building materials such as aminoacids and sugars, and in metabolic and regulatory processes in which enzymes and specific receptors are involved. As a consequence, the presence of a chiral center in drugs and bioactive agents in general implies large differences for the enantiomers both in the activity in the strict sense, and for metabolic conversion and pharmacokinetics in general.

Structural requirements for the biological activity often imply the presence of one or more chiral centers in the drug. Many of them are marketed as racemates. The enantiomers must, particularly from the biological point of view, be regarded as different substances. The neglect of stereochemistry in the development and application of drugs and bioactive agents in general leads to serious misconceptions and is a source of problems in pharmacokinetics.

At first view, symmetry is a very common phenomenon in nature. On the molecular level, however, asymmetry dominates as illustrated by the chirality of amino acids and sugars and by the stereospecificity of enzymatic reactions, drug-receptor interaction, etc. This holds true for the whole field of biology. It counts also for various types of messenger molecules, such as neurotransmitters, hormones, allosteric modulators of enzyme activity, as well as for xenobiotic, exogenous, messenger molecules such as drugs, insecticides and weedkillers. These transfer specific information, chemically coded in suitable molecular carriers, into biological objects.[1] Stereoselectivity in action is common. Chirality is not a requirement for bioactivity but in those cases, and there are many, in which a chiral centre is present in the bioactive molecule, usually great differences are found for the activities of the enantiomers. Understanding of the processes involved will be helpful in the development of more active and selective agents and particularly in the proper use of therapeutics and of bioactive agents in general.

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No doubt, the selectivity in action is based on a chemical complementarity between the messenger molecule or pharmacon and its specific receptor-site, the site of binding on the receptor molecule. In this complementarity, besides the physicochemical characteristics of the groups in the molecule which participate in the interaction, also their spatial arrangement, (their sterical configuration), is essential. Stereospecificity in action can be counted for on the basis of as few as three binding groups in the molecule, a three-point interaction.[1,2,3,4,5,6]

The isomers do not differ in their chemical properties in solution. Once bound to the specific, that is "stereoselective", site of action differences between the stereoisomers show up.

Separation techniques too are based largely on stereoselective "binding" of one of the isomers to a proper substrate. This holds also true for stereoselective analytical methods, such as radio-immuno- and radio-receptor assays[7] and chromatography via stereoselective adsorbents. In this respect also enantioselective determination based on derivatization with an enantiomer of a chiral, possibly labeled or fluorescent, reagent opens perspectives.[8,9] The two enantiomers in the racemic drug then form, usually easily separable and detectable, diastereoisomers.

Another possibility is the use of pseudoracemates, 1:1 mixtures of deuterated (+) and non-deuterated (−) or non-deuterated (+) and deuterated (−) isomers.[55,69] Since there is plenty of evidence that deuterated and non-deuterated compounds often are metabolized in a different, even stereospecific, way[70,71,72] there are restrictions. This technique is only valid if the deuterium is located in a stable position, free of metabolic attack.

If more than one center of asymmetry is located in one bioactive molecule (the case of diastereoisomers) and in other cases of geometric isomers such as: cis-trans-isomers, chair and boat configurations, epimers, isomerism on basis of intramolecular sterical hinderance, etc. as a result of differences in the intramolecular relationship between the various groups in the isomers, these will differ physicochemically. Therefore, as a rule such isomers are more easily separated than the enantiomers of compounds with a single center of asymmetry. Separation of the latter is still a laborious task.

In organic synthesis, normally enantiomers are obtained in a proportion 1:1. For geometric isomers this proportion depends on the synthetic procedure. Products of biological origin, such as hormones, antibiotics, etc. as a rule are obtained in stereospecific form. Largely for economic reasons, synthetic products such as drugs, insecticides, weed killers and in general in-

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dustrial products usually are marketed as racemic mixtures. The users, such as physicians, and in certain cases even the producers, too often unknowingly or unaware apply mixtures of compounds (stereoisomers) in the supposition that just one compound is involved.[2]

ISOMERIC BALLAST

In case of stereoselectivity in action only one of the components in the mixture, the racemate, is truly active. The biologically more active isomer is termed the eutomer, the less or inactive isomer the distomer. This is so regardless of their *-d-* and *-l-* or *-R-* and *-S-* configuration but with regard to a particular biological action. The degree of stereospecificity, that is the ratio of the activities (affinities, potencies, etc.) of the enantiomers is termed the eudismic ratio.[2,4,6] The distomer in the mixture should be regarded as an impurity, or "isomeric ballast", not contributing to the effect aimed at. It, however, potentially contributes to the unwanted effects, the side-effects and toxicity.

In medicine, there apparently is not too much concern about carrying along with e.g. 50 mg of the agent with the therapeutic action, 50 mg of a second agent with no contribution to the desired effect, although potentially harmful. For certain types of therapeutics, such as β-adrenergic agents, β-adrenergic blockers, anti-epileptics and oral anticoagulants, up to 90% of the products on the market are in fact racemic mixtures. For antihistaminics, anticholinergics, and local anesthetics, this holds true for about 50%, while on the whole it concerns 20 to 25% of the therapeutics.[11] In certain cases the differences in activity of the enantiomers are well established.[2,4,5,10,12,13,14,15]

In other cases no information is available. The implications of the use of mixtures of active and inactive isomers become clearer if one considers application of, for instance, pesticides. Neglect of the "isomeric ballast", the inactive isomer, constitutes a risk. Its presence implies chemical pollution—be it of the milieu interne of man and animals—or of the environment in general. Taken into account the growing apprehension on chemical pollution, one has to be well aware of this situation.

The remarkable discrepancy between on one hand the high degree of purity required for pharmaceuticals and on the other hand the acceptance of 50% impurity, as long as isomeric ballast is involved should be a matter of serious concern.

One at least might require that the presence of this impurity is harmless. Time is ripe to consider marketing of really pure drugs.

Techniques for stereoselective synthesis and separation of enantiomers by means of stereoselective anorganic- and biocatalyst are rapidly developing.[16,17,18,19,20,21,22,22a,22b]

ACTIONS OF "INACTIVE" ISOMERS

If only one of the enantiomers (the eutomer) is responsible for the desired biological e.g. therapeutic action there is no reason why not the, in this sense inactive one (the distomer) could be active in a different way. There is a whole spectrum of possibilities in this respect, many of which have been confirmed experimentally.

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1. One isomer has the therapeutic action, the other one contributes to the side-effects, or even is the main source thereof. *d*-Ketamine is predominantly hypnotic and analgetic. The *l*-isomer is the main source of unwanted side-effects.[23] The anorectic action of Fenfluramine, a racemate, in use now for about 15 years is located in the S(+)-enantiomer recently marketed as dextrofenfluramine (Isomeride®). This is twice as active and has less disturbing side-effects (dizziness, drowsiness, and sedation) reported for the racemate and to be ascribed to the "inactive" R(−)-enantiomer.[31]
2. Both isomers contribute to the main effect such as the local anesthetic action of the isomers of prilocaine while only one contributes to the hemotoxicity.[24]
3. One of the isomers may have an additional advantageous action like in the case of bupivacaine. Both isomers are local anesthetics but only one, the (−)-isomer shows a vasoconstrictive action.[25]
4. The therapeutically non-active isomer counteracts a side-effect of the therapeutically active isomer. In the diuretic indacrinone *d* is diuretic and causes uric acid retention, *l* acts as an uricosuric. It antagonizes the uric acid retention brought about by the diuretic isomer. This is not as effective as it looks since the "natural" proportion 1:1 between the compounds, the isomers, in a mixture as a rule is far from optimal. A study of various mixtures shows that a proportion of 1*d*:8*l* is optimal[26] (Fig. 1). Comparable relations are found for the isomers of the diuretic tienilic acid.[27]
5. The isomers may have opposite effects. In some barbiturates the *l*-isomer is a depressant, the *d*-isomer a convulsant (Fig. 2).[28,29]

Another example are the optical isomers of 1.4-dihydropyridine (BAY K8644). The (+)-(4R)-enantiomer being a calcium entry-blocker while the (−)-(4S)-enantiomer promotes the calcium influx.[29a] In some cases isomers act as competitive antagonists of each other. Mutual interaction between the enantiomers occurs. Dependent on the affinities of the isomers to their common sites of action the racemic mixture acts as a partial agonist.[2] In the narcotic analgetic picenadol *d* acts as an agonist, *l* as an antagonist, the racemate, *dl*, as a partial agonist.[30] Similar relationships are reported for other agents,[1,32,33] among which pheromones[34] and auxine-type plant growth substances.[35]

In those cases that the enantiomers have an affinity to common receptors but differ in their intrinsic activity the racemate will behave as a "pseudo" partial agonist. The characteristics thereof depend on the affinities and intrinsic activities of the individual enantiomers. In case of a racemic mixture composed of an agonist and a competitive antagonist with equal affinities to the receptors at saturation thereof with the racemate, only 50% will be activated.[35a,35b,35c]

6. The isomers may have advantageous complementary action like in the case of the α-β-adrenergic blocking "pseudohybrid-drugs."[36]
7. Stereoselectivity may be restricted to only one component in the biological action. The β-adrenergic blocking action of the β-blockers is stereoselective the non-specific cardiodepressant and the local anesthetic action is not. This indicates a difference in the mechanisms of

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