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"Atropisomeric" Drugs: Basic Concept and Example of Application to Drug Development

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Abstract

Many therapeutic drugs are racemates; *i.e.* they are chiral molecules consisting of "left"- and "right-handed" enantiomers (stereoisomers that are mirror images of each other, and are non-superimposable). In some cases, both enantiomers of the drug contribute to some extent (or equally) to the therapeutic effect; in other cases they contribute not at all. The same is true for the adverse effects of racemate drugs: the adverse effects of a racemate drug can be greater-than, less-than, or equal to one or the other enantiomer. An unusual situation arises when a drug consists of "atropisomers", stereoisomers arising because of hindered rotation about a single chemical bond. We summarize the concept of atropisomerism, and give examples.

Keywords

Atropisomer, Chirality, Pharmacotherapy, Drug Development, $Na_V1.7$ Inhibitor

1. Atropisomerism

Atropisomerism relates to chemical structures that contain at least two rings linked by a single bond. Normally, the free-energy of rotation is very low in such cases, so the rings are free to rotate about the axis of the bond. But if the rings have constituent groups sufficiently large, bulky, or otherwise repulsive, rotation can be inhibited, and create asymmetry. This situation gives rise to distinct non-interconvertible forms that are "rotational isomers" termed "atropisomers" (from the Greek for *the unturning*, after the eldest of the three Fates ætropoç, Atropos). The first atropisomers were identified for the compound 6,6'-Dinitro-2,2'-diphenic acid (**Figure 1**) [1].
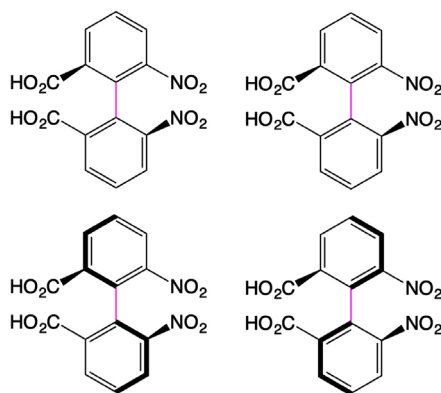
Figure 1. 6,6'-Dinitro-2,2'-diphenic acid. The two aromatic rings are joined by a single bond, which would normally allow the rings to rotate freely around the axis of the bond. But the carboxyylic and nitro groups sterically interfere with rotation, leading to non-superimposable "atropisomers". *Top*: usual representation of chemical structure; *Bottom*: heavy lines indicate that the aromatic ring is not planar.

Some examples of naturally-occurring atropisomers that have medicinal properties and are used in pharmacotherapeutic applications include the relatively small chemical structure of the selective inhibitor of leukotriene metabolism knipholone (**Figure 2**) [2] obtained from the roots of the tropical ferns *Kniphofia foliosa* to the very large chemical structure of the antibiotic vancomycin (**Figure 2**) [3] obtained from the soil bacterium *Amycolatopsis orientalis* (*Streptomyces orientalis*).

2. Relation to Drug Development

Chirality is of well-recognized importance in medicinal chemistry and drug development because mirror-image molecules often have clinically significantly different pharmacologic properties [4] [5] [6]. The enantiomers of a chiral drug can differ in pharmacodynamics or any aspect of ADME (absorption, distribution, metabolism, or elimination). And each of the enantiomers can be pharmacologically inert, or contribute (additively, synergistically, or sub-additively) to the drug's therapeutic effect or adverse effects [4]. If one enantiomer does not significantly contribute to the desired pharmacologic effect, it has been called "isomeric ballast" [7] [8]. Widely-used drugs that benefit from the contribution of both enantiomers are the analgesic tramadol [9] [10] [11] and the antidepressant fluoxetine [12] [13] [14]. A particularly tragic example of a negative contribution of an enantiomer to a drug is thalidomide [15] [16] [17].

In the case of compounds with classical chiral centers, interconversion of enantiomers requires bond-breaking. In contrast, in the case of atropisomers, interconversion involves only rotation around a bond (**Figure 3**). Thus, for atropisomers, the question becomes one of relative stability of the two forms. That is, the greater the steric hindrance inhibiting free rotation, the more stable—and less interconvertible—the individual forms (**Figure 4**). The relevant stability for pharmacotherapeutic use has to be assessed at body conditions, since the interconversion is pH and temperature-dependent [18] [19].
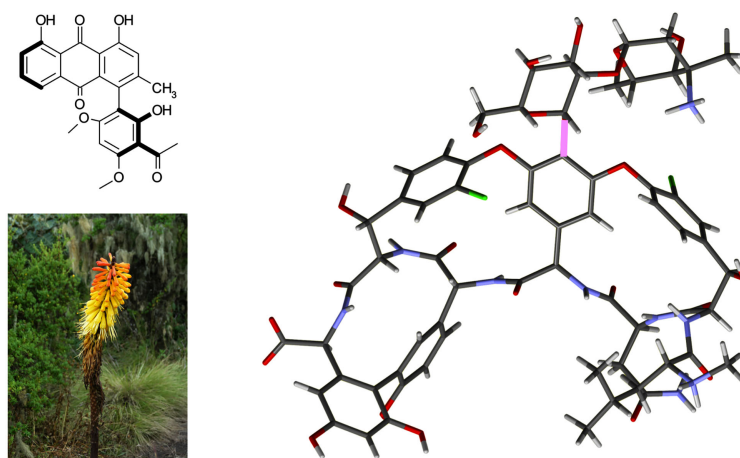
Figure 2. *Left*: knippholone from *Kniphofia foliosa*. *Right*: vancomycin from *Amycolatopsis orientalis*.
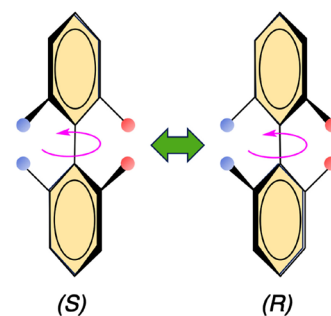

Figure 3. Rotation around the bond yields interconvertible forms (atropisomers). (*S*) and (*R*) are the stereochemical configurations according to the standard Cahn-Ingold-Prelog system.
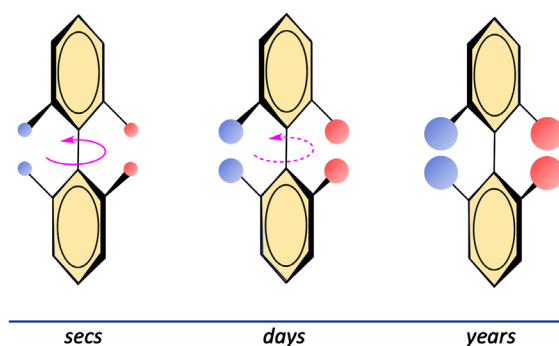

Figure 4. Greater steric hindrance increases the time of conversion from one chiral form to other. Different colors designate different constituent groups.

The complexities inherent in dealing with atropisomers in drug synthesis and development hindered enthusiasm for such compounds as drugs, but recent technical advances have spawned new interest [20]-[26] (**Figure 5**). As just one example, Takahashi *et al.* [27] introduced atropisomerism to a series of *N*-benzoylated indole derivatives of indomethacin and isolated stable atropisomers with different selectivity for cyclooxyhenase COX-1 and COX-2 isozymes.
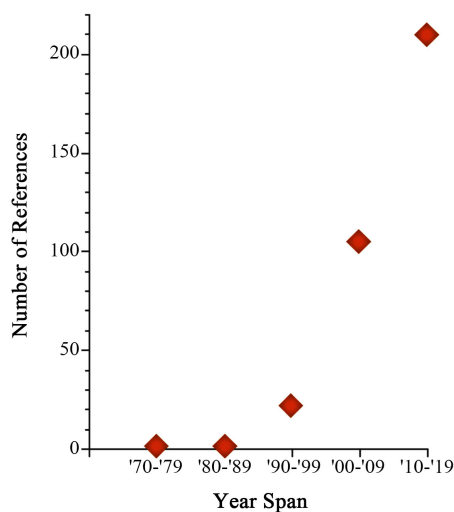
Figure 5. Number of publications listed in MedLine for the search term "atropisome(s)".

3. Atropisomeric Na$_V$1.7 Inhibitors

Na$_V$1.7 is the designation for one member of a family of sodium channels consisting of at least nine known members [28] [29]. They are proteins differentially located within certain cell membranes, and form transmembrane ion channels with selectivity for Na$^+$ ions [29]. Because of their location in dorsal root ganglia and other sites relevant to pain sensation transmission, mutations in the gene that encodes Na$_V$1.7 in humans (SCN9A) are linked to hereditary pain disorders [30] [31] [32], and loss-of-function mutations are associated with congenital insensitivity to pain [33], the Na$_V$1.7 type has been a favored target of analgesics drug discovery research [34] [35] [36] [37] [38] (**Figure 6**).

As an example, as part of a program to optimize the potency and reduce some negative ADME characteristics related to the pharmacokinetics and CYP450 metabolism of a series of selective sulfonamide Na$_V$1.7 inhibitors [39], Graceffa *et al.* [40] synthesized a series of atropisomeric quinolinone sulfonamide Na$_V$1.7 inhibitors. Several compounds had high affinity (nM) and selectivity for Na$_V$1.7, with improved pharmacokinetic and metabolic characteristics. One particular compound (AM-0466) showed antinociceptive activity in mice in a capsaicin-induced pain model. The analgesic pharmacologic characteristics of the atropisomer quinolone sulfonamide Na$_V$1.7 antagonist AMG8379 (**Figure 7**) were reported by Kornecook *et al.* [41]. It demonstrated dose-related activity in several Na$_V$1.7-dependent endpoints *in vivo*.

4. Summary and Conclusions

Atropisomerism is a less well-known type of chirality. Because the conversion of one form to the other involves rotation about a single bond, it can be relatively facile and occur in the timeframe of seconds. But, depending on the atropisomer's size and shape (steric bulk), electronic properties, and external factors
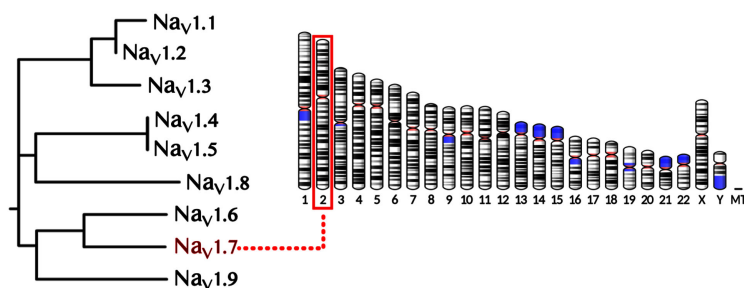
Figure 6. Putative evolutionary relationship among the Na$_V$1.x sodium channels and mapping to human chromosome 2. From Wikipedia.

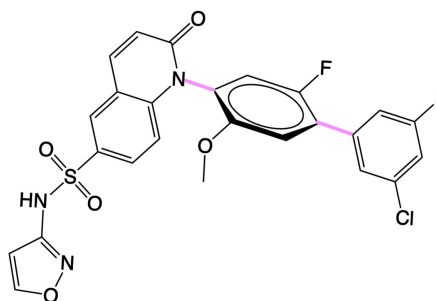**Figure 7.** Chemical structure of AMG8379, an atropisomer Na$_V$1.7 antagonist.

such as pH and temperature, one chiral form might not easily convert to the other form, and only do so so slowly (e.g. hours or even years) that the individual forms are essentially non-interconvertible. The recognition of, and an interest in, atropisomeric pharmacotherapeutics have increased in recent years, and several atropisomeric compounds have shown desirable properties over their non-chiral counterparts.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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