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Atropisomerism

The Challenge of Atropisomerism in Drug Discovery**

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atropisomerism · chirality · conformers · drug discovery · kinetics

The modern pharmaceutical industry is profoundly affected by chirality: it is well established that enantiomers may differ significantly in biological activity, pharmacokinetics, and toxicity.[1] The cases of thalidomide[2] and perhexiline,[3] whose enantiomers differ dangerously in effect or metabolic properties, emphasize the importance of addressing stereochemistry in drug development. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) indicate a preference for chiral drugs to be developed as single enantiomers in cases when this gives improved safety and/or efficacy.[4] However, there are drugs in which mixtures of enantiomers have acceptable toxicological profiles (for example ibuprofen is sold as a racemic mixture).[5] These policies, and the fact that single enantiomer drugs often offer superior biological activity, have meant that 65% of new drugs released between 2004 and 2006 were single enantiomers—made possible by advances in asymmetric synthesis and separation technologies[6]—while only 7% were racemic or mixtures of diastereoisomers.[5]

Herein, we address the pharmaceutical implications of a hitherto largely overlooked alternative source of drug chirality: atropisomerism.[7] Atropisomers are conformers which, owing to steric or electronic constraints, interconvert slowly enough (by definition, with a half life of >1000 s) that they can be isolated.[7,8] The stereochemical consequences of hindered rotation about a single bond can be such that an apparent single compound can actually be a mixture of two, or an apparently achiral compound can actually be racemic. If such pairs of stereoisomers are separable, then the implications for drug discovery may be similar to those of compounds with classical chiral centers. In the context of a lack of standard procedures for dealing with atropisomerism, and the absence of specific regulatory policies governing conformationally based stereochemistry, we explore some recent examples of atropisomeric compounds that have been or are in drug development. We also draw conclusions relating to potential strategies for design and development where atropisomerism is an issue. We expose and propose options for the management of atropisomerism, which, many view as a lurking menace with the potential to significantly increase the cost of pharmaceutical research and development if ignored.

Atropisomerism may give rise to geometrical isomers, diastereoisomers, or enantiomers, all with the distinctive feature that they can in principle be equilibrated thermally. In the absence of specific regulatory policies, atropisomeric stereoisomers are best dealt with in the same way as stereoisomers with classical chiral centers, but with isomerization rates and, where necessary, differential conformer populations taken into account. For racemic drug candidates, the FDA policy statement from 1992 emphasizes the importance of understanding the main therapeutic activities of the isomers through in vitro or in vivo studies. Studies of the pharmacokinetic behavior of the individual enantiomers carried out early in the development of drug candidates are also valuable. Knowledge gained from these studies can help guide the choice of development of a single enantiomer versus a racemic mixture. Development of a drug as a racemic mixture may be appropriate if the mixture is not reasonably separable (by synthetic methods, HPLC analysis, etc.) or if racemization is rapid in vitro and/or in vivo (as in ibuprofen or thalidomide), thus making it futile to administer only the eutomer (more active isomer). However, it is nonetheless highly recommended that critical pharmacological attributes related to the safety and efficacy of both isomers is investigated: overall, there must be an acceptable toxicology profile and a suitable therapeutic window (in vitro, in animal models, and in humans).

By analogy, similar considerations should also be applicable to atropisomers. Given the potential for equilibration, two main strategies can be adopted: a) if the barrier to atropisomerisation is high, develop an atropisomeric drug as a single, pure, stereochemically stable isomer, or b) if the barrier to atropisomerisation is low, develop the drug as a consistent and reproducible interconverting mixture.

Telenzepine (**1**; Scheme 1), which is a selective muscarinic antagonist useful for the treatment of peptic ulcers,[9] presents

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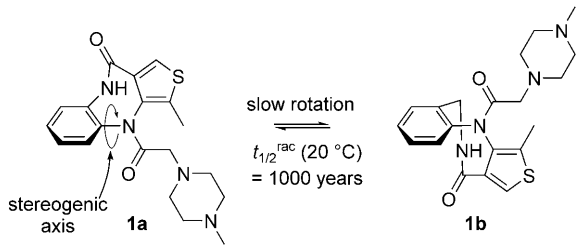
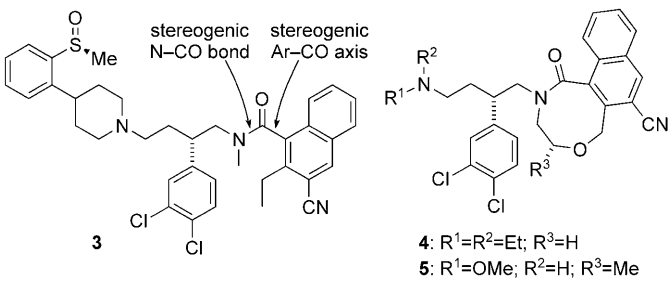


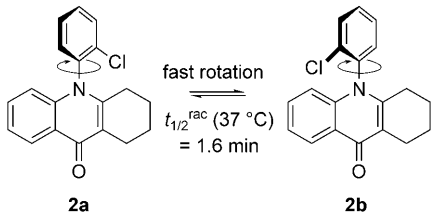
Scheme 1. Slow interconversion between the atropisomeric enantiomers of telenzepine (**1**).



Scheme 3. NK1 antagonist lead structure **3** with modifications **4** and **5**.

an example of the first strategy. Telenzepine is atropisomeric, with a stereogenic C–N axis, and at 20 °C in neutral aqueous solution it displays a half-life for racemization of the order of 1000 years. Partial separation of the enantiomers **1a** and **1b** was achieved by exploiting their difference in affinity for muscarinic receptors. The (−)-isomer turned out to be inactive and has a have much lower selectivity than the (+)-isomer; a 500-fold difference in activity between the atropisomers was seen at muscarinic receptors in rat cerebral cortex.

Conversely, in Sch 40120 (**2**; an inhibitor of 5-lipoxygenase useful for treating acute inflammatory diseases such as psoriasis) a mixture of interconverting conformers was developed.[10] Like telenzepine, Sch 40120 has a stereogenic axis arising from hindered rotation along a C–N bond (Scheme 2). Its enantiomers **2a** and **2b** can be observed by HPLC on a chiral stationary phase, but they interconvert with a half-life of only 1.6 minutes at 37 °C, thus making the atropisomers separable at ambient temperature or below, but not in vivo. It was therefore argued that the unavoidably short half-life of each enantiomer justified the development of a racemic, rather an enantiomerically pure drug.



Scheme 2. Fast interconversion between the atropisomeric enantiomers of Sch 40120.

The decision to develop a drug candidate as a purified enantiomer or as a racemate should be in place as early as possible during the lead optimization stage. For example, researchers at AstraZeneca identified the NK_1 antagonist **3** (Scheme 3) as a potential treatment for depression.[11] However, **3** exhibited restricted rotation about two bonds, and four diastereoisomeric atropisomers were observed by HPLC analysis and NMR spectroscopy. These atropisomers had half-lives measurable in days at 37 °C and were amenable to separation and isolation, thus allowing them to be structurally characterized and their activities to be established in vivo. A precedented[12] geared rotation about both the Ar–CO and N–CO bonds selectively interconverts the atropisomers **3a** and **3d** or **3b** and **3c** (Scheme 4).

The existence of multiple atropisomeric forms would certainly complicate drug development, so early in the development process these stereochemical complexities were eliminated. The group from AstraZeneca found that the activity of NK_1 in vivo resulted from atropisomer **3a**; therefore a more rigid conformational mimic of the bioactive atropisomer **3a** was designed. Compound **4** resulted from linking the amide and the naphthyl groups in an eight-membered ring, thereby locking the amide unit in the desired bioactive *trans* configuration. This compound displayed high potency and selectivity, but was still found to exist as a mixture of two diastereoisomeric atropisomers about the Ar–CO bond, which interconvert with a half-life of 9.7 hours at 37 °C. Further modification provided **5**, in which the additional stereogenic centre imposes predominantly a single conformation on the Ar–CO axis. Compound **5** possesses excellent potency in vitro and in vivo.

Another related approach has been to modulate the rate of axial bond rotation—to engineer faster bond rotation such

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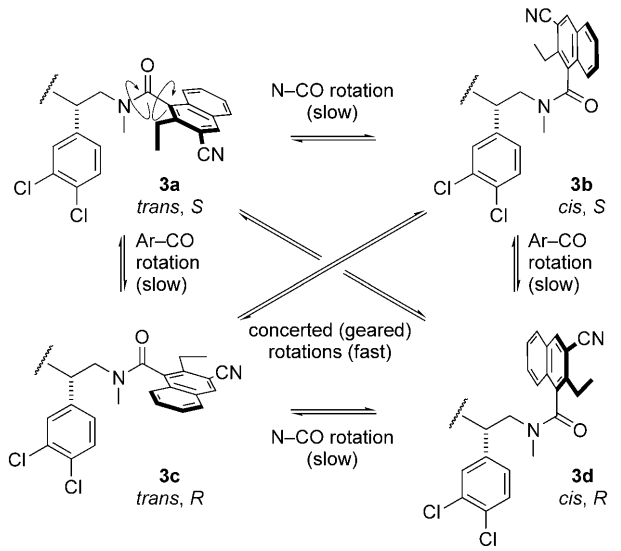


Scheme 4. Selective interconversion between diastereoisomeric atropisomers of **3**.

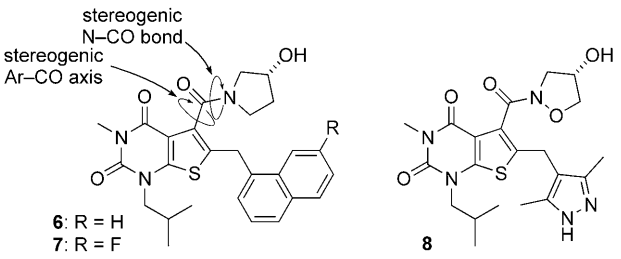
that atropisomers no longer exist. Compounds **6** and **7** (Scheme 5) were found to be effective monocarboxylate transporter (MCT1) blockers and exhibited favorable properties.[13] Slow rotation about the N–CO and Ar–CO bonds resulted in four separable diastereoisomeric atropisomers. All were shown to have different potencies, but their rates of interconversion—with half-lives of 1 to 12 hours at 37 °C—made acceptable control of the atropisomer ratio impossible under physiological conditions.

Consequently, analogues of **6** and **7** with isomerization half-lives of less than 15 minutes were sought. Compound **8**, in which the pyrrolidine group was replaced by an isoxazolidine unit and the naphthalene group by a pyrazole unit, no longer exhibited atropisomerism: its conformers interconverted rapidly and it had acceptable druglike properties.

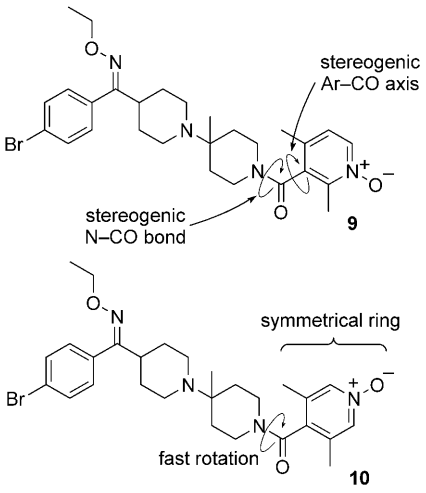
The existence of atropisomers can also be avoided by symmetrization. As part of an HIV drug discovery program, researchers at Schering-Plough were interested in developing small molecule CCR5 antagonists that inhibit viral entry into host cells.[14] These studies resulted in the clinical candidate Sch 351125 (**9**; Scheme 6) which was shown to reduce levels of HIV-1 RNA in infected patients. However, restricted bond rotations meant that Sch 351125 existed as a mixture of four atropisomeric stereoisomers (i.e. a pair of racemic diastereoisomers).[14a] All four stereoisomers showed antiviral activity, with a 15-fold difference between the best and the worst stereoisomer, and displayed half-lives for interconversion of the order of 5 hours at 37 °C. The strategy used by the group at Schering-Plough to circumvent this problem was to prepare symmetrical amide analogues such as **10**. Symmetry at the Ar–CO bond eliminates diastereoisomerism, and although enantiomeric conformers still exist because of restricted rotation around the N–CO bond, they interconvert rapidly. These symmetrized compounds exhibited comparable efficacy in binding and viral entry assays, but their overall profiles were inferior to the parent molecule, and work is reportedly ongoing to identify superior candidates.[14b]

Atropisomeric properties are not always immediately evident: while BMS-207940 (**11**)[15] and LY-411575 (**12**)[16] are hindered biaryls, and are unsurprisingly atropisomeric under certain conditions, similar conformational properties are more disguised in the structures of quinoxalinedione **13**,[17] the HIV integrase inhibitor **14**,[18] and the Bcl-2-ligand **15**[19] (Scheme 7). Aside from biaryls, hindered aryl amides are frequently characterized by slow conformer interconversion, as are medium rings (as in the biologically active natural products colchicine and vancomycin, both of which exhibit atropisomeric properties[20]).

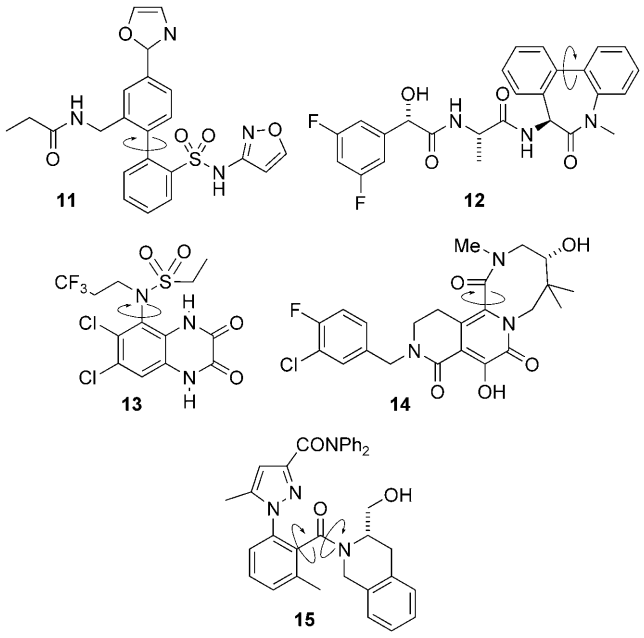
To summarize the situation, it is evident that pharmaceutically interesting compounds which are compact and heavily substituted may possess more than one kinetically stable and stereochemically distinguishable conformation. Whether these conformations interconvert on the millisecond or millennium time scale, potential problems in design, development, and marketing must be carefully considered and surmounted in order to produce and market stable, consistent drug substances. Recognizing the existence of atropisomerism in compounds of interest is an important first step, and rates of conformer interconversion must be monitored throughout the development pathway (using dynamic NMR methods,chiral HPLC analysis, chiral shift reagents, etc.). It is also prudent to consider the potential for differential metabolism of atropisomers. Understanding the properties of the atropisomers in the solid state (e.g., potential for segregation during crystallization or interconversion during storage) may be used to develop improved quality control processes. The



Scheme 5. Atropisomeric drug candidates **6** and **7** and a non-atropisomeric replacement **8**.



Scheme 6. The CCR5 antagonist Sch 351125 (**9**) and symmetrical amide analogue **10**.



Scheme 7. Hindered rotation in BMS-207940 (**11**), LY-411575 (**12**), quinoxalinedione **13**, HIV integrase inhibitor **14**, and Bcl-2 ligand **15**.

FDA website provides some useful guidance to their expectations for drug development in this context.[4]

Options for dealing with the phenomenon of atropisomerism can be implemented at the early stage of drug design. For example, it may be possible to make related analogues that have the following features: 1) symmetry about a hindered bond, thus eliminating a chiral axis; 2) faster rotation about a hindered bond, thus pushing the half-life for conformational interconversion down to the order of seconds; 3) further encumbrance about a hindered bond to produce separable atropisomers whose interconversion is negligibly slow (for example, half-lives of the order of millennia); or 4) introduction of a stable stereogenic centre to perturb the population of interconverting atropisomers such that only one desirable conformation predominates.

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