PUTTING CHIRALITY TO WORK: THE STRATEGY OF CHIRAL SWITCHES

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Most of the new drugs reaching the market today are single enantiomers, rather than the racemic mixtures that dominated up to ten years ago. Many of the new single-enantiomer drugs were developed as such, but there are also important examples of new single-enantiomer drugs derived from 'chiral switches' of established racemates. Indeed, a well-timed chiral switch can offer enhanced therapy and further profitability as a 'line extension' of a major racemic drug with patents that are expiring.

CHIRALITY
The geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superimposable on its mirror image; such an object has no symmetry elements of the second kind (a mirror plane, $\sigma = S_1$; a centre of inversion, $i = S_2$; or a rotation–reflection axis, S_{2n}). If an object is superposable on its mirror image, it is described as being achiral.

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"*And should not I spare Nineveh, that great city, wherin are more than sixscore thousand persons that cannot discern between their right hand and their left hand; and also much cattle*".

Book of Jonah, Chapter 4, Verse 11

The issue of drug CHIRALITY is now a major theme in the design, discovery and development of new drugs, underpinned by a new understanding of the role of molecular recognition in many pharmacologically relevant events[1–7]. There are two principal scenarios in chiral drug development: the *de novo* development of an enantiomerically pure drug, or a switch from an existing racemic drug to one of its isomers in a pure form[8]. Single-enantiomer drugs are a rapidly growing proportion of new drugs that are introduced to the market, rising from ~20% of new drugs ten years ago to almost 75% today. Today, 'chiral switches'[9–13], which exploit single enantiomers of existing RACEMATES (racemic mixtures), are an important feature of drug development portfolios. Although they have limited application in the generic marketplace, they are increasingly being used to allow 'line extensions' of blockbuster drugs — for example, omeprazole. There are now several examples of well-timed switches of racemic drugs that have PATENTS that are about to expire — rapid and economical 'bridging' strategies have been devised to allow efficient development and speedy regulatory approval of switched single enantiomers (see FIG. 1 and the definitions in the margins for the basic terminology of stereochemistry[14,15]).

Emergence of chirality in drug development

One of the main features of the living world is its chirality[14,16,17] (FIG. 2). CHIRAL CENTRES are common in the amino-acid and carbohydrate building blocks of proteins, carbohydrates and nucleic acids. These biomolecules are made up of units that have the same sense of chirality — the 21 essential amino acids are all L-enantiomers, whereas most carbohydrates have the D-CONFIGURATION. Essential physiological processes are, therefore, homochiral — they show 100% STEREOSELECTIVITY and only involve one of all the possible stereoisomers of key molecules[18]. When exogenous compounds are introduced into the body, physiological processes show a high degree of chiral distinction (a term that is preferred to chiral discrimination)[19], with the effects of different stereoisomers often being markedly different as a consequence of their differential interaction with chiral targets, such as receptors, enzymes and ion channels.

After decades of essentially two-dimensional pharmacology and therapeutics, in which the pharmacopoeia was dominated by racemates, the early 1980s saw a rediscovery of stereochemistry[5]. This was driven by the emergence of new technologies that allowed the preparation of pure enantiomers in quantity, leading to a renewal of interest in the stereochemistry of drug action[7]. In parallel, advances in stereoselective bioanalysis led to a new awareness of the importance of stereoselective pharmacokinetics and drug disposition[7]. It was realized that most drugs were actually mixtures of stereoisomers, which were divided by Ariëns into the eutomer — in which the desired effects are concentrated — and the

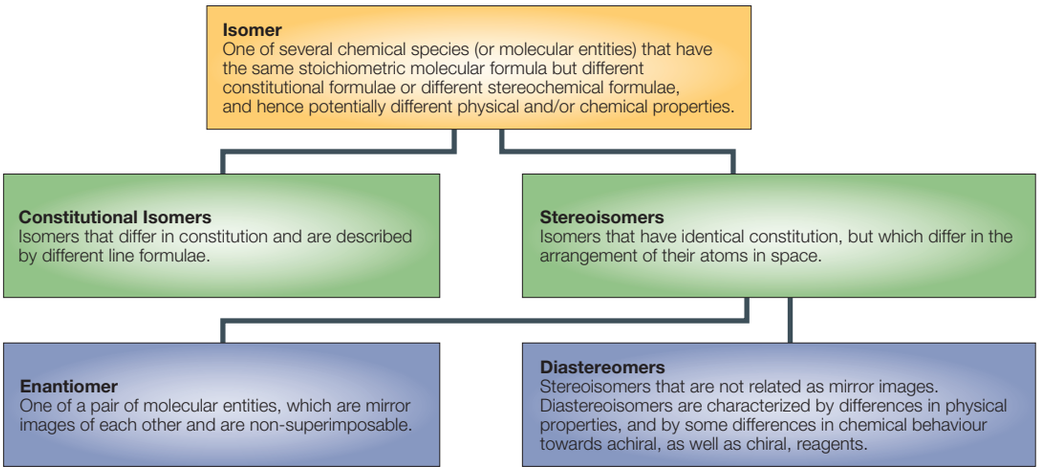


Figure 1 | **Basic terminology of stereochemistry.**

CONFORMATION
The spatial arrangement of the atoms affording distinction between stereoisomers, which can be interconverted by rotations about formally single bonds. A conformer is one of a set of stereoisomers, each of which is characterized by a conformation that corresponds to a distinct potential energy minimum.

CONFIGURATION
In the context of stereochemistry, the term is restricted to the arrangements of atoms of a molecular entity in space that distinguishes stereoisomers, the isomerism between which is not due to conformational differences. The absolute configuration is the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description — for example, *R* or *S* (for chiral centres) and *M* or *P* (for chiral axes).

RACEMATE
An equimolar mixture of a pair of enantiomers. It does not have optical activity. The chemical name or formula of a racemate is distinguished from those of the enantiomers by the prefix (±)- or *rac*- (or *racem*-), or by the symbols *RS* and *SR*.

PATENT
A grant by the state of exclusive rights for a limited time (in most jurisdictions 20 years from filing date) in respect of a new and useful invention. The patentable invention must be new, it must involve an inventive step and it must be capable of industrial application.

CHIRAL CENTRE
(Chirality centre). An atom that holds a set of ligands in a spatial arrangement, which is not superimposable on its mirror image. A chiral centre is, therefore, a generalized extension of the concept of the asymmetric carbon atom to central atoms of any element.

D,L
Configurational descriptors for carbohydrates and α-amino acids.

distomer, which is at best an inactive 'isomeric ballast' and at worst, the molecule in which toxicity is concentrated[20]. The experience of the past 15 years has allowed us to move from this rather simplistic distinction to an appreciation of the differentiation of the relative contributions of stereoisomers to overalldrug action[1,5,21]. If one enantiomer is responsible for the activity of interest, its paired enantiomer could be inactive, have some activity of interest, be an antagonist of the active enantiomer, have a separate activity of interest or have a separate and undesirable activity[1,5,22].

Figure 2 | **Study of Praying Hands, by Albrecht Dürer (1508).** An example of non-superimposable mirror images. Reproduced with permission from the Albertina, Vienna, Austria © (2002).

As these scenarios emerged, it became clear that the failure to address issues raised by the stereochemistry of racemic drugs was the cause of some drug–drug interactions, severe adverse reactions and withdrawals from the market. It further became evident that the use of stereochemically pure drugs should be advantageous, as they would be expected to reduce the total dose given, simplify the dose–response relationship, remove a source of intersubject variability and minimize toxicity due to the inactive stereoisomer[5]. These pharmacodynamic and pharmacokinetic factors led to an increasing preference for single enantiomers in both industrial and regulatory circles. The data in FIG. 3 show a clear trend towards single-enantiomer new chemical entities (NCEs), both in development and in those compounds reaching regulatory approval, which began in the late 1980s, when a marked preference for defined stereoisomers of new drugs was established[23]. Worldwide sales of chiral drugs in single-enantiomer forms continued to grow at an annual rate of >13% in 2000 to US $133 billion, and by 16.7% in 2001 to US $147.2 billion. 40% and 36% of all drug sales in 2000 and 2001, respectively, were of single enantiomers, compared with 33% in 1999 (REF. 11). The debate about the relative merits of racemates and single enantiomers was short lasting, and it was resolved emphatically in favour of the latter[5,21]. An analysis of the new molecular entities (NMEs) that were approved by the US Food and Drug Administration (FDA) in 1998–2001 gave the following approximate distribution: 52% achirals; 30% single enantiomers with several chiral centres; 7% single enantiomers with one chiral centre; 7% racemates; and 4% multiple diastereomers[24] (see Center for Drug Evaluation and Research (CDER) website). This distribution indicated that there is a significant proportion of racemates among recently approved NMEs. A similar picture was revealed from an analysis of the 95 NCEs assessed by the UK Medicines Control Agency (MCA) in 1996–2000, which gave the following distribution: 36% achirals; 48% single enantiomers; and 16% racemates[25,26] (FIG. 3).

The chiral-switch concept

Chiral switches are chiral drugs that have already been CLAIMED, approved and marketed as racemates or as mixtures of diastereomers, but have since been re-developed as single enantiomers[9]. The definition of a chiral switch can be broadened to include chiral drugs that have been approved already as mixtures of diastereomers, such as EPIMERS, but have since been developed as single enantiomers, or single enantiomers (E_1) that have been redeveloped and launched as the paired enantiomer (E_2). The essential criterion of a chiral switch is a change in the status of chirality. We prefer the term chiral switch to racemic switch because the switch is usually from a racemic drug ($E_{1,2}$) to the corresponding single enantiomer(s) (E_1 and/or E_2). An alternative term that could be used is 'enantiomer switch'. The definition also allows a switch to a non-racemic mixture of enantiomers[27,28]. The chiral-switch concept is illustrated in FIG. 4.

Rationale for the chiral switch

When the concept first emerged, the chiral switch was seen as an opportunity for manufacturers of generic or branded products to develop new products from the old racemates of innovative companies. However, despite the regulatory acceptance of bridging strategies from racemate to enantiomer, few successful switches have emerged from this route. It seems that there is a considerable premium attached to the database for the racemate, which has hindered several switches. Instead, we have seen several successful switches emerge from the innovators of racemic drugs that have provided relatively low-cost line extensions for blockbuster drugs[12,29,30]. Strategies for the timing of such switches are important. It is preferable to introduce the new, switched, single-enantiomer product onto the market immediately before the expiration of the racemic patent, so that the new and enhanced product can be introduced before competition from generic forms of the old racemate affects sales. Interestingly, and contraty to accepted thinking, a chiral switch would not have prevented the thalidomide tragedy (BOX 1).

International regulation and patentability

International regulation. The rapid emergence in the 1980s of a scientific consensus on the importance of stereochemistry in drug development was matched by a regulatory response. The guidelines in the major jurisdictions[25,31–34] differ in fine detail, but four common features are clear. Applicants must recognize the occurrence of chirality in new drugs, attempt to separate the stereoisomers, assess the contribution of the various stereoisomers to the activity of interest and then make a rational selection of the stereoisomeric form that is proposed for marketing. These common features are the basis for the consideration of this topic under the auspices of the International Conference on Harmonisation[35]. The guidelines also refer to the concept of the chiral switch as discussed in this article, and allow the development of bridging strategies, in which data about the racemate can be used to support the licensing of one of its component enantiomers.

Single enantiomers as new chemical entities. In the United States, a single enantiomer of a previously approved racemate is not considered to be an NCE[34,36], as it contains a previously approved active moiety[37] (an NCE or NME is defined as an active ingredient that has never been manufactured in the United States). The FDA assigns a chemical type (CHE)[37] to chiral switches to new drug products on a case-by-case basis, and the results are not consistent. For example, esomeprazole magnesium (Nexium) and levobupivacaine hydrochloride (Chirocaine) were classified as new derivatives of existing drugs (CHE2), whereas

STEREOSELECTIVITY
The preferential formation in a chemical reaction of one stereoisomer over another. When the stereoisomers are enantiomers or diastereomers, the phenomenon is known as enantioselectivity or diastereoselectivity, respectively.

CLAIM
The part of a patent specification that defines the scope of protection.

EPIMERS
Diastereomers that have the opposite configuration at only one of two or more tetrahedral stereogenic centres that are present in the respective molecular entities.

PATENTABILITY
The basic conditions of patentability, which an application must meet if granted, are that the invention must be novel, contain an inventive step, be capable of industrial application and not be in one of several exluded fields.

NOVELTY
The essential condition for patentability that what is claimed is new.

INVENTIVE STEP
An invention is taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter that forms part of the state of the art, but not including matter from a patent application with an earlier priority date that is published later then the priority date of the invention (European Patent Convention, Section 3). The state of the art is the total information in the relevant field known to the hypothetical person skilled in the art.

INSUFFICIENCY
A ground of invalidity of a patent, if the description does not allow the skilled reader to work the invention.

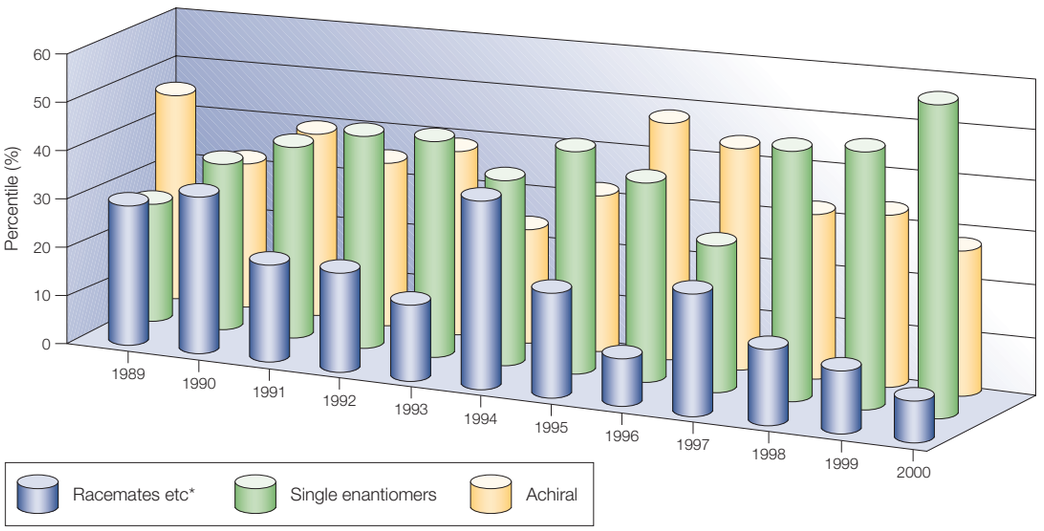


Figure 3 | **Annual distribution of worldwide approved drugs according to chirality character (1989–2000).** Data obtained from REF. 23.* Including diastereomeric mixtures.

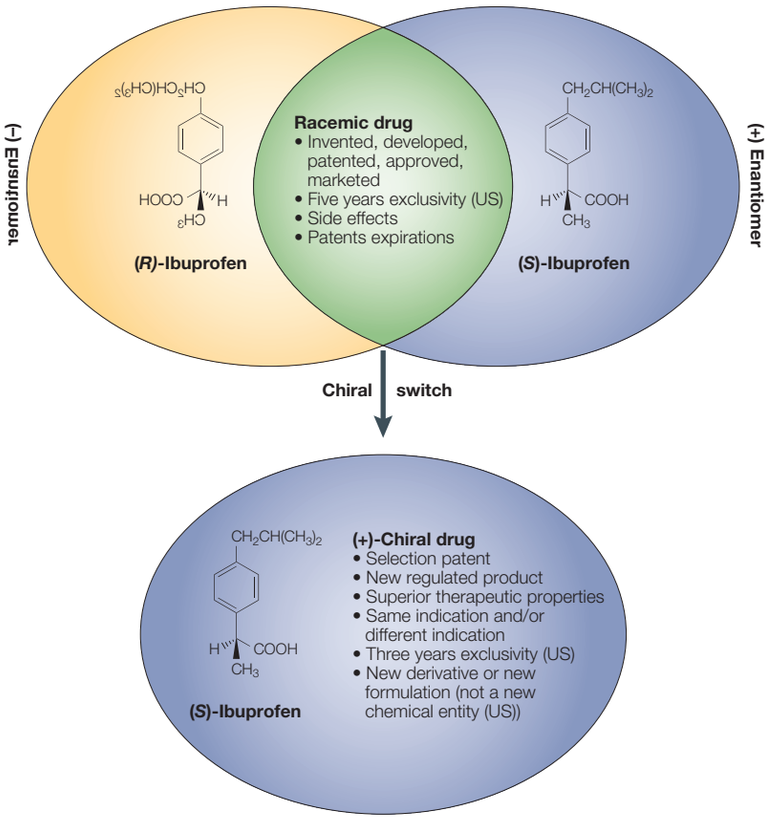


Figure 4 | **The chiral-switch concept.**

dexfenfluramine (Redux), levofloxacin (Levaquin), levalbuterol (Xopenex), dexmethylphenidate (Focalin) and escitalopram oxalate (Lexapro) were classified as new formulations (CHE3) (see FIG. 5 for the structures of these molecules). It is important to note that none of these approved chiral switches was classified as an NME (CHE1). So, chiral switches are barred from the five years of exclusivity that is granted to new drugs, and are eligible for only three years exclusivity after further clinical investigations are carried out[34,38–40].

Patentability of chiral switches. The prerequisites for PATENTABILITY are that the protection claimed is NOVEL, INVENTIVE and of industrial applicability, and that the supporting description is 'SUFFICIENT'[41,42] (see margins for basic definitions of patent terms[41]). In the United States, the bulk of the legislative implementation of the statutory provisions that cover the various aspects of patents are found in the Patent Act of 1952, Title 35, United States Code (35 USC)[43]. In the European Union, the relevant legislation is embodied in the European Patent Convention (EPC)[44], which has been in force since 1977. When the two enantiomers of a chiral drug are sufficiently different in pharmacological effects from each other and from the racemate, it might be possible to obtain a patent for one or both enantiomers, in addition to a valid (or expired) patent of the corresponding racemate. Leading relevant legal precedents in the United States and the European Union are quoted in BOX 2.

Chiral switch as a selection invention. A selection invention is an invention that selects a group of new members from a previously known class on the basis of superior properties[41,45]. Selection patents are governed by the I.G. Farben rules[41,45,46], and are also recognized by European patent law[47]. The patentability of enantiomer(s) in a chiral switch is an extreme case of the patentability of a selection invention[9]. In the DuPont (Witsiepe) judgement[48], the House of Lords in the United Kingdom held that the disclosure of a class — even a very small class, such as a racemate — whether in general terms or by enumeration of its members, is not a disclosure of the individual members so as to make them no longer new. A case in point is the selection patent[49] of the antibacterial single-enantiomer drug amoxycillin from a previously claimed group of nine semi-synthetic penicillins[50] that originated from three CONSTITUTIONAL isomers, each one giving rise to the respective (+)-epimer, (–)-epimer and their 1:1 mixture[51]. Amoxycillin is (+)-(1*S*,2*S*,5*R*,6*R*)-6-[*R*-2-amino-2-(*p*-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (FIG. 5). The selection patent claimed a pharmaceutical composition that had been adapted for oral administration to human beings, which contained amoxycillin. The Court of Appeal in England upheld the validity of the amoxycillin method-of-use selection patent[51].

The strategy of enantiomeric pairs of patents. Consider the two enantiomers E_1 and E_2 of a racemic drug $E_{1,2}$, and their patents. The strategy of obtaining enantiomeric pairs of patents for single enantiomers in a chiral-switch scenario involves two patents. In the first patent, the claim is that E_1 is pharmacologically superior to $E_{1,2}$. In the second patent, the claim is that E_2 is pharmacologically superior to $E_{1,2}$. Both patents have identical PRIORITY DATES. The patents of E_1 and E_2 are an enantiomeric pair of patents of single enantiomers. This strategy allows the proprietor to simultaneously 'dance in two weddings', with the advantage of avoiding or postponing the decision about which single enantiomer to develop. A second party might discover that E_1 is pharmacologically superior to E_2. However, the utility of E_1 is already claimed by one of the two original patents and is, therefore, covered. This is probably a case of a discovery and not of an invention. So, the expectation that the second party will be able to obtain a patent for its claims is very small. In cases in which a company holds INTELLECTUAL PROPERTY rights to single enantiomers or to pairs of enantiomers in a chiral-switch scenario, the original proprietor of the patents of the corresponding racemate (or other interested parties) might be obliged to negotiate with that company to obtain licenses for these patents. The strategy of obtaining enantiomeric pairs of patents for single enantiomers has been adopted by Sepracor in many chiral switches, and has proved to be particularly successful in the United States[9].

Are enantiomeric pairs of patents of single enantiomers true or false? Such patents might, in principle, be true, if diastereomeric homochiral and heterochiral

CONSTITUTION
The description of the identity and connectivity (and corresponding bond multiplicities) of the atoms in a molecular entity (omitting any distinction that arises from their spatial arrangement).

PRIORITY DATE
The date on which an invention was first disclosed to a patent office in a patent application or in an earlier application from which it validly claims priority.

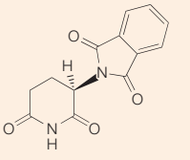
INTELLECTUAL PROPERTY LAW
An area of the law that concerns legal rights that are associated with creative effort or commercial reputation and goodwill.

Box 1 | **The thalidomide tragedy: the myth of a missed opportunity**

The thalidomide tragedy of 1961 is a landmark in drug regulation. Thalidomide is a racemate — of a glutamic-acid derivative — and in 1984, in the foreword of a book about X-ray crystallography[130], the following statement appeared: "The thalidomide tragedy would probably never have occurred if, instead of using the racemate, the (*R*)-enantiomer had been brought on to the market. In studies … it was shown that after i.p. administration only the (*S*)-(–)-enantiomer exerts an embryotoxic and teratogenic effect. The (*R*)-(+)-enantiomer is devoid of any of those effects under the same experimental conditions". This quote has been widely used subsequently, and was even alluded to in the citation for the 2001 Nobel Prize in Chemistry, which was awarded to Knowles, Noyori and Sharpless for the development of catalytic asymmetric synthesis, and has had a great impact on the development of new drugs[131].

Regrettably, the proposal that the thalidomide tragedy could have been avoided if the single enantiomer had been used is misleading, for two reasons. First, it is based on unreliable biological data: the studies purporting to show that (*S*)-(–)-thalidomide is more teratogenic were in the mouse — a species that is generally regarded as unresponsive — and involved very high doses[132]. However, earlier work in the rabbit, the species that is most sensitive to thalidomide, showed clearly the equal teratogenic potency of its enantiomers[133]. Second, the chiral centre in thalidomide is unstable in protonated media and undergoes a rapid configurational inversion[134].

So, the individual enantiomers of thalidomide are both inverted rapidly to the racemic mixture and also degraded rapidly by opening of the glutarimide ring — processes that occur faster *in vivo* than *in vitro*[135]. Therefore, even if there were differences in the toxicity of the enantiomers of thalidomide, their rapid racemization *in vivo* would blunt them such that they could not be exploited. This case shows the importance of considering data in full and not leaping to conclusions, however tempting these might be.



***(R)*-(+)-Thalidomide**

interactions are involved and can be differentiated; that is, $E_1 \cdots E_1$ and/or $E_2 \cdots E_2$ (homochiral interactions) compared with $E_1 \cdots E_2$ (heterochiral interactions)[14]. However, the experimental evidence to support the claims in such enantiomeric pairs of patents is scarce. We propose that it is not sufficient to claim that, for a given chiral drug, both enantiomers E_1 and E_2 have superior pharmacological effects (for example, lack of adverse effects) compared with the corresponding racemic drug $E_{1,2}$, without claiming that E_1 is superior to E_2 (or vice versa). The examiners of the European Patent Office (EPO), contrary to the US Patent and Trademark Office (PTO) examiners, have so far declined to grant enantiomeric pairs of patents. The EPO has been concerned about the strategy of applying for enantiomeric pairs of patents. Examples are the enantiomeric pairs of Sepracor's method-of-use patents[52,53] for the single enantiomers of cisapride for the treatment of gastro-oesophagial reflux disorder and other disorders that are associated with the digestive tract (BOX 3). The applications are under consideration and litigation in the EPO[54]. The examining division of the EPO decided in July and August 2001 to refuse the applications. Appeals to these decisions have been filed.

Launched chiral switches: successes

TABLE 1 lists the launched chiral switches in 1994–2002.

Omeprazole to esomeprazole. In commercial terms, probably the most important chiral switch so far has been the switch from the blockbuster gastric anti-secretory proton pump (H^+/K^+-ATPase) inhibitor (PPI) omeprazole (Losec, Prilosec)[55,56] to esomeprazole magnesium (Nexium)[56–59]. Omeprazole, which was launched in 1988 by Astra AB, was the world's highest-selling drug, and had worldwide annual sales of US $6.2 billion in 2000 (REF. 60). The first patents on omeprazole expired in the European Union in 1999 and in the United States in 2001. There are three other marketed chiral PPI drugs that are structurally related to omeprazole: lansoprazole (Privacid, Zoton), pantoprazole (Protonix, Protium, Pantozol) and rabeprazole (Aciphex, Pariet), were launched in 1991, 1994 and 1997, respectively, and all have similar therapeutic profiles[56] (FIG. 6).

Omeprazole is a racemate. Its chirality stems from the presence of a chiral centre at the sulphur atom of the methylsulphinyl bridge between the 1*H*-benzimidazole and the pyridine moieties. Omeprazole is in fact a prodrug, acting as a PPI by means of the 'omeprazole cycle', which involves achiral intermediates[61,62] (FIG. 6). At present, there are litigation proceedings about the validities of many omeprazole patents in the United States and other jurisdictions[63].

Two main issues have confronted AstraZeneca in considering the development of a chiral switch of omeprazole. First, omeprazole is an excellent drug, in terms of both efficacy and safety — the chiral switch would, therefore, have to lead to a single enantiomer that is markedly superior to fulfil the criteria of patentability of a chiral switch, but also to compete effectively with cheaper generic versions. Second, the mechanism of action of omeprazole involves achiral intermediates, including the active form sulphenamide, which attacks the H^+/K^+-ATPase[61,62]. This raises the question of whether single enantiomers of omeprazole would be more susceptible to acid activation and would have improved pharmacokinetic and metabolic properties that would give an improved

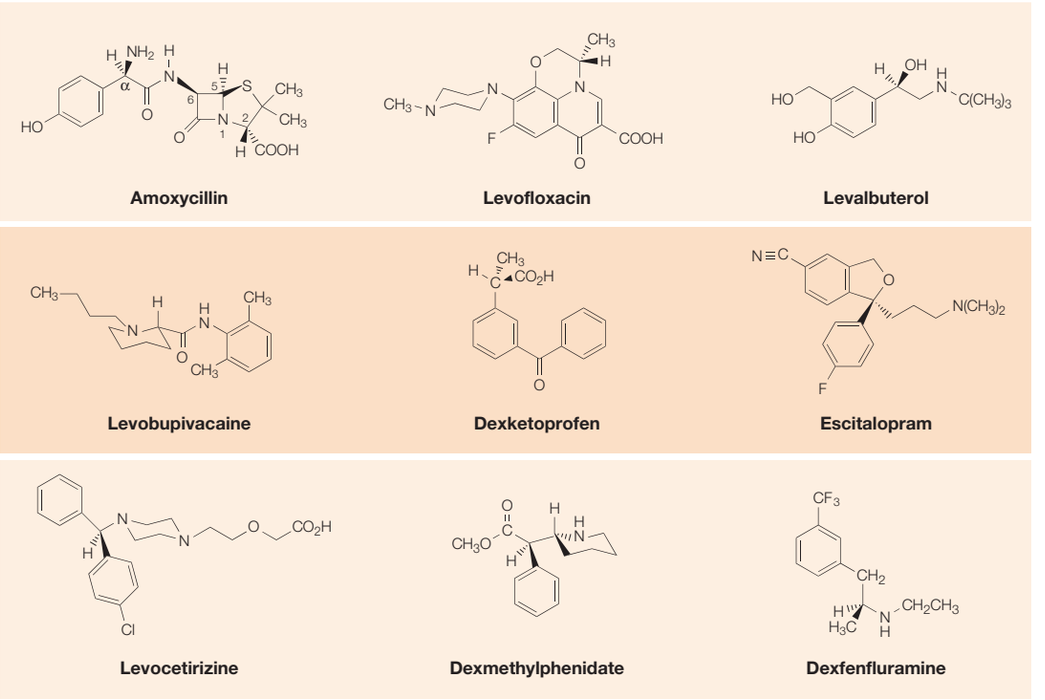


Figure 5 | **Structures of launched single-enantiomer drugs.**

therapeutic profile. Esomeprazole magnesium ((*S*)-(–)-omeprazole magnesium) was approved for use across the European Community by the Mutual Recognition Procedure in July 2000, and was launched throughout Europe under the tradename Nexium from August 2000 onwards. It was approved in the United States in February 2001, and was launched there in March 2001. Healing of reflux oesophagitis with a 40 mg per day dose of esomeprazole magnesium occured in ~78% of patients after four weeks of treatment and in 93% of patients after eight weeks, compared with 65% and 87% of patients, respectively, treated with 20 mg per day of omeprazole[64,65]. Esomeprazole is completely metabolized by the cytochrome P450 system, mainly by the polymorphic isoform CYP2C19, which is responsible for the formation of the 5-hydroxymethyl and desmethyl metabolites[64,65].

Omeprazole undergoes polymorphic metabolism[64–66]. Approximately 3% of Caucasian individuals and 15–20% of Oriental individuals are slow metabolizers of omeprazole. Reducing inter-individual variation in plasma levels and effect would be of therapeutic benefit, and esomeprazole has been shown to be an improved alternative to omeprazole as its clearance is less dependent on CYP2C19 than the racemate. The mean plasma concentration (area under the curve; AUC) slow/AUC rapid ratios for (*R*,*S*)-omeprazole, (*S*)-omeprazole and (*R*)-omeprazole were 1/10, 1/3 and 1/30, respectively[65,66]. Although the other racemic PPI drugs are structurally related to omeprazole, they do not contain the 5-methyl substituent at the pyridine ring, and, therefore, are not prone to 5-methyl hydroxylation by CYP2C19. Hence, their single enantiomers are not expected to have polymorphic inter-individual variation in their metabolism.

The landmark patent that claims (–)-omeprazole[67] was issued on 3 February 1998 to Astra AB with a priority date of 28 May 1993 on the basis of a Swedish patent application. This patent describes a process for the manufacture of (–)-omeprazole, but also claims pharmaceutical compositions that comprise an alkaline salt of (–)-omeprazole and a carrier. It protects all pharmaceutical compositions that comprise (*S*)-omeprazole, irrespective of the way in which the compound has been prepared, and contains a method-of-treatment claim for the use of the compound in the treatment of gastric-acid-related diseases. This was followed by a process patent[68] (dated 7 July 1998) and a method-of-use patent in the United States (dated 2 March 1999)[66], both issued to Astra AB. The latter patent claimed a method for treating gastric-acid-related desease by inhibition of gastric secretion, in which (*S*)-(–)-omeprazole is administered to decrease inter-individual variation in plasma levels of gastric acid (AUC). This shows the application of the criterion of 'non-OBVIOUSNESS' (inventiveness) in chiral switches.

These patents were preceded by US Patent 5,693,818 (dated 2 December 1997, issued to Astra AB), which claimed Na^+, Mg^{2+} and other salts of (+)- and (–)-omeprazole and processes for their preparation[69]. The Mg^{2+} salt of (*S*)-omeprazole trihydrate, processes of its preparation and its method of use for treating gastric-acid-related conditions are claimed in WO Patent 98/54171 (dated 3 December 1998)[70]. The separation

OBVIOUS
Capable of being preformed by the average skilled person in possession of the prior art.

of the enantiomers of omeprazole in analytical scale was described in REF. 71 and the synthesis of single enantiomers of omeprazole on preparative scales were described in a German patent[72] (dated 14 May 1992), which was issued to Byk Gulden and Lomberg Chemische Fabrik GmbH with the priority date 8 November 1990.

The case of esomeprazole highlights the importance of timing of the chiral-switch strategy. When the chiral switch is developed by the proprietor of the racemate, it is advantageous for the single enantiomer to reach the market before the expirations of the patents of the racemate, and before the incursion of the respective generic drugs. This was the case with esomeprazole. In the present context, the pricing policy is important. TABLE 2 gives the prices of the PPI drugs, including esomeprazole, in the United Kingdom and the United States in July 2001. The price of the recommended dose of esomeprazole (40 mg per day)[65] was lower than that of omeprazole (20 mg per day), even though its (*S*)-omeprazole ratio is ~4:1. The companies that market the competing PPI drugs might have a vested interest in the success of esomeprazole, in spite of the fact that it is in competition with their own drugs. So, the success of the chiral-switch product serves as a fence against the lowering of the prices of all the branded PPIs.

Omeprazole has been described and claimed in its patents as 5-methoxy-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-sulfinyl]-1*H*-benzimidazole. In July 2001, three patents were issued to aaiPharma that describe the complex nature of omeprazole[73–75]. Since then, five other US patents pertaining to pharmaceutically active compounds of the benzimidazole family, including omeprazole, have been issued to aaiPharma[76–80]. The patented invention is that in omeprazole, which was considered to be a racemate, two constitutional isomers are present in the solid state — the 5-methoxy- and 6-methoxy-1*H*-benzimidazole derivatives — and their ratios vary with the method of manufacture. A method of preparing the pure 6-methoxy-1*H*-benzimidazole derivative was also claimed. Furthermore, in addition to the chiral centre at the sulphinyl sulphur atom, the patents disclose that omeprazole contains a CHIRAL AXIS at the pyridine ring due to the spatial orientation of the 4-methoxy-3,5-dimethylpyridine moiety and the hindered rotation of the 4-methoxy substituent. So, each of the two constitutional isomers gives rise to two pairs of enantiomers: (*R*,*P*)/(*S*,*M*) and (*R*,*M*)/(*S*,*P*). The two constitutional isomers are tautomers; they undergo fast isomerization in solution. It remains to be seen whether the courts will validate the above aaiPharma patents. *Ab initio* density functional theory (DFT)-optimized

CHIRAL AXIS
(Chirality axis). An axis about which a set of ligands is held so that it results in a spatial arrangement that is not superimposable on its mirror image.

OPTICAL ACTIVITY
A sample of material that can rotate the plane of polarization of a beam of transmitted plane-polarized light is said to have optical activity (or to be optically active). This optical rotation is the classical distinguishing characteristic (which is sufficient but not necessary) of systems that contain unequal amounts of corresponding enantiomers. An enantiomer that causes rotation in a clockwise direction (when viewed in the direction that faces the incoming light beam) under specified conditions is called dextrorotatory and its chemical name or formula is designated by the prefix (+)-; one causing rotation in the opposite sense is laevorotatory and is designated by the prefix (–)-. Materials that have optical activity also have other chiroptic phenomena.

PRIOR ART
All public knowledge before the priority date that could be relevant to the novelty or unobviousness of an invention.

Box 2 | **Leading legal precedents on patentability of a single enantiomer in a chiral switch**

Re: May and Eddy. US Court of Customs and Patent Appeals. US CCPA 574F.2d1082, 197 USPQ 601 (1978).
"*The novelty of an* OPTICAL *isomer is not negated by the* PRIOR ART *disclosure of its racemate … It was totally unexpected that appellants' leavo and α-leavo N-methyl benzomorphans would have exhibited such a combination of properties [analgesic potency comparable to morphine coupled with nonaddictiveness] and, concomitantly, could be used to effect nonaddictive analgesia*"[136].

Eli Lilly and Company versus Generix Drug Sales Inc. *et al.* 460F. 2nd 1096, US Court of Appeals for the Fifth Circuit. 174 USPQ (BNA) 65 (1972).
"*We reject the contention that the patent on the α-*DL *racemic mixture here did not protect the use of the α-*D *isomer for analgesic purposes once it was later established that the isomer was the repository of the useful and novel invention claimed … the optical isomer in which the asserted quality lay cannot be utilized without infringing the patent on the racemic mixure … The fact that the α-*L *isomer proved to be inoperable as an analgesic did not make this claim invalid*"[137].

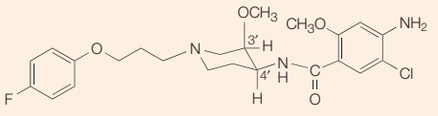
Enantiomers/HOECHST. European Technical Board of Appeals Decision. T 296/87 — 3.3.1 (1988).
"*Long before the contested patent's priority date, it was generally known to specialists that, in physiologically active substances (for example, herbicides, fungicides, insecticides and growth regulators, but also pharmaceuticals and food stuffs) with an asymmetrical carbon atom enabling them to occur in the form of a racemate or one of two enantiomers, one of the latter frequently has a quantitatively greater effect than the other or than the racemate. If — as here — the aim is therefore to develop agents with increased physiological activity from a physiologically active racemate the obvious first step … is to produce the two enantiomers in isolation and test whether one or the other is more active them the racemate. Such tests are routine. Under established Board case law, an enhanced effect cannot be adduced as evidence of inventive step if it emerges from obvious tests … The novelty of the* D- *and* L- *enantiomers is not destroyed by the description of the racemate*"[138].

SEPRACOR. European Technical Board of Appeals Decision. T 1031/00 — 3.3.2 (2002).
"*The appellant relied heavily, as novel features, on the absence of side effects of the therapy of claim 1 using the (–) isomer of amlodipine … The Board considers that this can only be regarded as the discovery of an additional item of knowledge about the known therapeutic application of (–) amlodipine for the treatment of hypertension but cannot in itself confer novelty on this known therapeutic application. To be novel, such a discovery would have to lead to a new therapeutic application or to the application of the known therapeutic application to a new group of subjects. That clearly not being the case here*"[139].

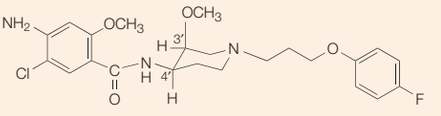
Box 3 | **The enantiomeric pair of Sepracor's patents of the single enantiomers of cisapride**

Patent WO 94/01111 (REF. 140)**, EP Patent Application 93918153.3** (REF. 52)
Applicant: Sepracor, Inc. (Marlborough, Massachusetts, USA)
Title: Methods of using (+)-cisapride for the treatment of gastro-esophageal reflux disease and other disorders
Claim 1: A method of treating gastro-esophageal reflux disease in a human while avoiding the concomitant liability of adverse effects associated with racemic cisapride, which comprises administering to a human in need of such treatment, an amount of (+)-cisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (–)-stereoisomer, said amount being sufficient to alleviate reflux disease but insufficient to cause said adverse effects.

Patent WO 94/01112 (REF. 141)**, EP Patent Application 93916996.7** (REF. 53)
Applicant: Sepracor, Inc. (Marlborough, Massachusetts, USA)
Title: Methods of using (–) cisapride for the treatment of gastro-esophageal reflux disease and other disorders
Claim 1: A method of treating gastro-esophageal reflux disease in a human while avoiding the concomitant liability of adverse effects associated with racemic cisapride, which comprises administering to a human in need of such treatment, an amount of (-)-cisapride, or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer, said amount being sufficient to alleviate reflux disease but insufficient to cause said adverse effects.



(3′*R*,4′*S*)-Cisapride



(3′*S*,4′*R*)-Cisapride

(B3LYP/ 6-31G(d)//B3LYP/6-31G(d)) extended and folded conformations of (*S*,*P*)- and (*S*,*M*)-omeprazole, respectively, are given in FIG. 7 (REF. 81).

The energy barrier for the (*S*,*P*) ⇌ (*S*,*M*) diastereomerization of esomeprazole is probably very low. AstraZeneca has elected non-exclusive licenses from aaiPharma to the above patents, but decided not to list them in the FDA Orange Book[82], which covers new patents on drugs that have previously been approved by the FDA. A listing in the Orange Book might give AstraZeneca the right to challenge generic versions of the drug that infringe on the new patents.

Albuterol to levalbuterol. Albuterol (known as salbutamol in Europe) is the leading bronchodilator, a β_2-adrenoceptor agonist that can increase bronchial-airway diameter without increasing heart rate. Albuterol is a racemate, and its bronchodilator activity resides in (*R*)-albuterol. (*S*)-Albuterol, however, is not inert, as it indirectly antagonizes the benefits of (*R*)-albuterol. There are pharmacokinetic differences between the enantiomers; (*S*)-albuterol being cleared more slowly. So, the potentially harmful (*S*)-enantiomer tends to accumulate in preference to the therapeutically effective (*R*)-enantiomer. These pharmacokinetic and pharmacodynamic differences provided the basis for the chiral switch of albuterol to levalbuterol ((*R*)-albuterol), which has the same indications as *rac*-albuterol, but has a superior side-effect profile[29,83].

Bupivacaine to levobupivacaine. The long-acting local anaesthetic bupivacaine has been in use for many years, mainly as a spinal and epidural anaesthetic for childbirth and orthopaedic procedures, such as hip-replacement surgery. Similar to other local anaesthetics, it acts by blocking Na^+ channels and also has actions on the heart, which restrict its use by intravenous injection for regional anaesthesia. In the United States, it carries a 'black box' warning on the label, which draws attention to an important side-effect problem. Bupivacaine is a racemate, and its (*S*)-(–)-enantiomer levobupivacaine has been developed successfully as a safer local anaesthetic that has the same therapeutic indications as the racemate[84,85]. The main achievement in this development programme was the decision by the FDA that levobupivacaine need not carry the black box warning that is required on the label of the established racemate[84].

The chiral switches of 'profen' NSAIDs. The most numerous class of non-steroidal anti-inflammatory drugs (NSAIDs) that is in use at present is the 2-aryl-propionic acids or 'profens', the first of which was ibuprofen, which was introduced into clinical use in 1969. NSAIDs are used widely for the treatment of inflammatory diseases, such as rheumatoid arthritis, as both analgesics and antipyretics. They account for ~5% of all prescriptions in the United Kingdom, but are responsible for more than 25% of all the adverse reactions reported to the MCA each year. These adverse reactions affect a range of organs, including (in decreasing order of importance) the gastrointestinal tract, kidney, bone marrow, respiratory system and liver. Several strategies have been used to try to reduce these toxicities, and these include exploiting two important aspects of the chirality of the profens, all of which have a chiral centre in the side chain. These drugs are all racemates, with the exception of naproxen, which was introduced to the market as the (*S*)-enantiomer.

Table 1 | **Launched chiral switches (1994–2002)**

Racemic drug		Single-enantiomer drug				
Generic name	***Brand name (company)***	***Generic name***	***Brand name (company)***	***Stereochemistry***	***Year launched/***	***Treatment/ indication jurisdiction***
Omeprazole	Losec, Prilosec (AstraZeneca)	Esomeprazole magnesium[57,58,64]	Nexium (AstraZeneca)	(*S*)-(–)-Omeprazole	2001 US	Gastric, anti-secretory
Ofloxacin	Floxin (Ortho-McNeil)	Levofloxacin[29,142]	Cravit (Daiichi), Tavanic (Aventis), Levaquine (Ortho-McNeil)	(*S*)-(–)-Ofloxacin	1995 JP	Antibacterial
Albuterol sulfate Salbutamol	Ventolin (Glaxo Wellcome)	Levalbuterol HCl[83]	Xopenex (Sepracor)	(*R*)-(–)-Albuterol	1999 US	Anti-asthmatic
Bupivacaine	Marcaine	Levobupivacaine[84,85] (Perdue Pharma; originator, Chiroscience)	Chirocaine	(*S*)-(–)-Bupivacaine	2000 US	Local anaesthetic
Ibuprofen	Advil	Dexibuprofen[87] (GebroBroscheck, Paz), DexOptifen (Spirig AG)	Seractil	(*S*)-(+)-Ibuprofen	1994 Austria	Anti-inflammatory, analgesic
Ketoprofen	Orudis, Oruvail (Wyeth)	Dexketoprofen trometarol[89]	Enantyum, Keral (Menarini)	(*S*)-(+)-Ketoprofen	1998 EU	Anti-inflammatory, analgesic
Cetirizine HCl	Zyrtec (UCB Pharma/ Pfizer)	Levocetirizine HCl[143]	Xyzal, Xusal (Sepracor/UCB Farchim SA)	(*R*)-(–)-Cetirizine	2001 EU	Allergy, antihistamine
Methylphenidate HCl ((*R,R*)-(+) , (*S,S*)-(-))	Ritalin	Dexmethylphenidate HCl[144]	Focalin (Novartis/ Celgene)	(*R,R*)-(+)-Methylphenidate	2001 US	ADHD
Citalopram HBr	Celexa (Forest Laboratories), Cipramil (Lundbeck)	Escitalopram oxalate[145,146]	Cipralex (Lundbeck), Lexapro (Forest Laboratories)	(*S*)-(+)-Citalopram	2001 EU	Antidepressant
Fenfluramine HCl	Pondimin (Servier, American Home Products)	Dexfenfluramine HCl[92]	Redux (Interneuron Pharmaceuticals, American Home Products)	(*S*)-(+)-Fenfluramine (withdrawn 1997)	1996 US	Antiobesity

Data obtained from REF. 23. ADHD, attention deficit hyperactivity disorder; EU, European Union; HCl, hydrochloride; JP, Japan, US, United States.

The primary biological action of the profens, as with other NSAIDs, is the inhibition of cyclooxygenases (COXs), the enzymes that are responsible for the first step in the synthesis of prostaglandins and other mediators from arachidonic acid. This underlies their anti-inflammatory, analgesic and antipyretic properties, which have been established in several animal models. COX inhibition resides exclusively in the (*S*)-enantiomer, as shown by *in vitro* studies in a wide range of test systems. However, the activities of the two enantiomers of many profens are essentially indistinguishable *in vivo*, owing to the fortuitous unidirectional metabolic bioconversion of the (*R*)-enantiomer to the (*S*)-enantiomer. The extent of this reaction differs between compounds and species, and in some cases, the inactive (*R*)-enantiomers are pro-drugs for the active (*S*)-forms. The combination of the stereospecificity of action of profens, together with the configurational inversion reaction provides a rationale for the use of the (*S*)-enantiomers of these drugs in therapy[86], as this reduces the total dose given, reduces toxicity that arises from non-stereospecific mechanisms or is associated with the (*R*)-enantiomer, and removes the rate and extent of inversion as a source of inter-individual variation in metabolism and pharmacological effect[87].

So far, chiral switches have been successful for two NSAIDs, ibuprofen and ketoprofen — the first based on chiral inversion and the second based on the stereospecificity of COX inhibition. Racemic ibuprofen undergoes rapid and substantial configurational inversion, so that the internal exposure is principally to (*S*)-ibuprofen, with little (*R*)-ibuprofen present in the circulation[87]. The (*S*)-ibuprofen that is present is derived from both the 50% of the racemate that is in that form and configurational inversion. Racemic ibuprofen and (*S*)-ibuprofen can, therefore, be viewed as being 'essentially bioequivalent', but the use of (*S*)-ibuprofen gives faster onset of action and reduces variability in configurational inversion as a source of variability in response. However, this switch has not been exploited in the main jurisdictions, largely due to difficulties in securing EU patent protection[88] and regulatory (FDA) approval as an over-the-counter medication (see FDA Arthritis Drugs Advisory Committee Meetings online). At present, (*S*)-(+)-ibuprofen (dexibuprofen) is available only in Germany and Austria (as Seractil), and Switzerland (as DexOprifen).

The (*S*)-(+)-enantiomer of the long-established NSAID ketoprofen is responsible for most of its pharmacological actions, and its selectivity for the COX-1

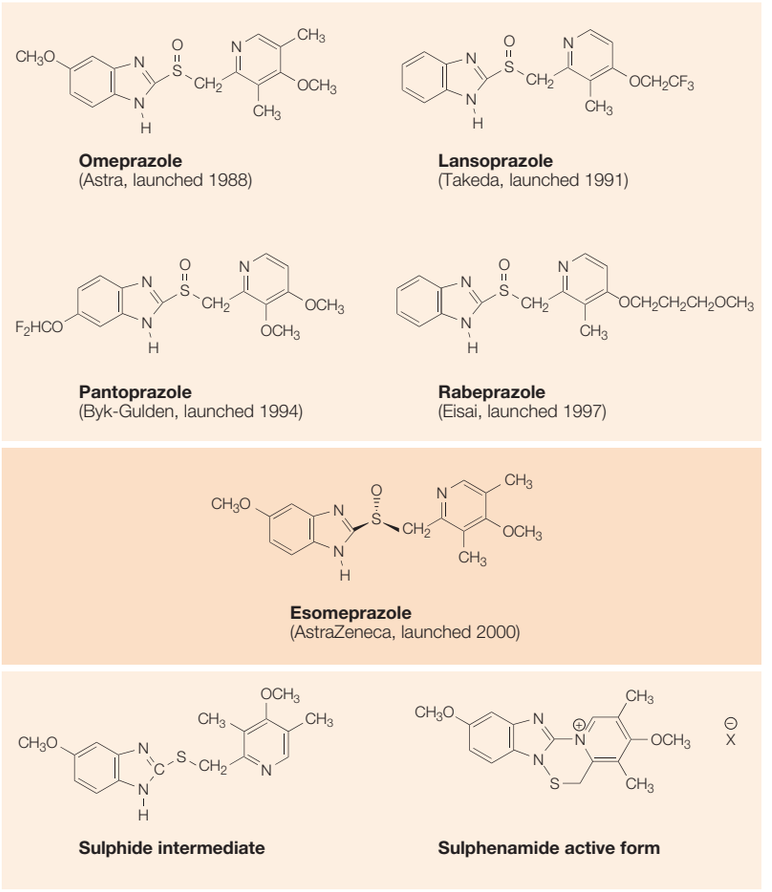


Figure 6 | **PPI drugs and achiral intermediates in the 'omeprazole cycle'.** PPI, proton-pump inhibitor.

and COX-2 isozymes is independent of the isomeric form. Unlike most other profens, the metabolic configurational inversion of ketoprofen is minimal in humans and animal species other than the mouse. As the (*R*)-enantiomer is not a pro-drug for the active (*S*)-form, the chiral switch is straightforward. Dexketoprofen is 2–4 times more potent than the racemate. To provide a further advantage for the single enantiomer, it has been formulated as a salt with tromethamine (dexketoprofen trometamol), which is more rapidly and extensively absorbed from the stomach than the free acid. The time to maximum plasma concentration (T_{max}) for dexketoprofen trometamol is 0.5 hours (range 0.3–1 hours), compared with 1.25 hours (range 0.5–3 hours) for the racemic free acid. The presentation of dexketoprofen as the tromethamine salt therefore provides three advantages: effective analgesia at lower doses (from the chiral switch), rapid onset, and reduced gastric irritation and improved tolerability (both resulting from the novel salt form)[89].

Chiral switches that failed to fulfil the promise

The 'Fen-phen' fiasco: fenfluramine to dexfenfluramine. Dexfenfluramine (FIG. 5) is the (*S*)-(+)-enantiomer of the racemic drug fenfluramine. 'Fen–phen' is a combination of fenfluramine and the achiral drug phentermine[90,91]. Fenfluramine was approved by the FDA in 1973 as an appetite suppressant for short-term anorectic treatment of obesity[91], and was marketed as Pondimin by Wyeth-Ayerst Laboratories, a division of American Home Products (now Wyeth). Phentermine was approved in 1959 for the short-term (a few weeks) treatment of obesity[91].

Dexfenfluramine was first developed and marketed in France by Servier. It was developed in the United States by Interneuron Pharmaceuticals, now Indevus Pharmaceuticals, and was marketed by Wyeth-Ayerst. The New Drug Application (NDA) of dexfenfluramine hydrochloride as a monotherapy for long-term use was approved by the FDA (as a new formulation) in April 1996, and it was launched in June 1996 as Redux[90–92], with the caveat that its safety beyond one year of administration had not been described[91]. Since the approval of dexfenfluramine, the 'fen–phen' combination has also been referred to the dexfenfluramine–phentermine combination. Both fenfluramine and dexfenfluramine seem to act by affecting the metabolism of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) in the brain[92]. US Patent 4,309,445 (REF. 93), entitled D-Fenfluramine for Modifying Feeding Behavior, was granted in January 1982; its continuation in part is US Patent 4,452,815 (REF. 94), entitled Method of Utilizing D,L-Fenfluramine for Modifying Feeding Behavior, which was granted in June 1984. The term of the latter patent subsequent to January 1999 has been disclaimed. Previous to these patents, neither (+)-fenfluramine nor (±)-fenfluramine were shown to reduce carbohydrate craving selectively. In June 1996, Interneuron Pharmaceuticals filed an application for an extension of US Patent 4,309,445 — which was scheduled to expire in 2001 — for abnormal carbohydrate craving, under 35 USC §156 (Hatch–Waxman Amendment, 1984)[95]. The objective of 35 USC §156 was to compensate the holder of a patent for a drug for the regulatory review period of the approved product. In December 1996, the FDA determined that dexfenfluramine was eligible for a patent extension[96]. In February 1997, the FDA notified the PTO Commissioner of the total length of the regulator-revised period for dexfenfluramine (1,613 days). The FDA told the PTO that the 'active ingredient' of dexfenfluramine was the (+)-enantiomer of fenfluramine[96]. The 'plain meaning' of the patent-term extension statute requires that a patent be found eligible for extension if the active ingredient of the 'product' that was subjected to the regulatory review period was not previously approved by the FDA[96]. In 1984, it was reported that the anorexigenic effects of fenfluramine could be duplicated and its side effects minimized by the use of the fen–phen combination[97]. A subsequent report by the same group confirmed the safety and effectiveness of the combination[98]. However, fen–phen has not been approved by the FDA.

In 1996–1997, approximately 18 million prescriptions were written in the United States for fenfluramine and phentermine, and more then 2 million for dexfenfluramine; ~5 million people in the United States have been

Table 2 | **Prices of PPI drugs (July 2001)**

Generic name	Trade name	UK price (£)*		US price ($)*		Company
		20 mg	40 mg	20 mg	40 mg	
Omeprazole	Losec, Prilosec	52.01	26.01‡	114.26	114.26	AstraZeneca
Esomeprazole magnesium	Nexium	33.69	52.01	107.83§	107.83§	AstraZeneca
Lansoprazole	Prevacid, Zoton	23.64¶	43.25#	118.26	113.53	Takeda Pharmaceuticals
Pantoprazole sodium	Protonix	23.46	48.07	83.75		Byk Gulden
Rabeprazole Sodium	Aciphex	22.64	41.43	105.92		Eisai

* per 28 units; ‡ per 7 units; § per 30 units; ¶ per 15 mg; # per 30 mg. PPI, proton-pump inhibitor.

exposed to these drugs[90,91]. The surge in the use of fenfluramine, dexfenfluramine and fen–phen in 1996 and 1997 and the establishment of the therapeutic niche for dexfenfluramine is (partially) attributed to the chiral switch of fenfluramine. In September 1997, the FDA and the manufacturers, acting on new evidence about significant side effects of valvular heart disease for fenfluramine and dexfenfluramine, with or without phentermine[99], announced the withdrawal from the market of fenfluramine and dexfenfluramine as treatments for obesity[91]. These drugs have also been linked to primary pulmonary hypertension[100]. At the time that dexfenfluramine was withdrawn, it was reasonable to expect that the US Commissioner of Patents would grant, on the basis of the recommendation of the FDA, the extension of US Patent 4,309,445 until 2003. So, the promising chiral switch of fenfluramine into dexfenfluramine was, in principle, successful both from the intellectual property point of view and from the regulatory point of view.

After the withdrawal of fenfluramine and dexfenfluramine, including fen–phen, product liability lawsuits have been filed against American Home Products and Interneuron Pharmaceuticals. A US $3.25 billion national class-action settlement for the users of the withdrawn drugs was approved by the US District Court in Philadelphia in August 2000, and was affirmed by the US Court of Appeals in August 2001 and by the US Supreme Court in January 2001. American Home Products took charges related to the fenfluramine/dexfenfluramine/fen–phen litigations of US $13.2 billion. In conclusion, the chiral switch of fenfluramine to dexfenfluramine highlights the practical inherence in a collaboration between the regulatory authority (FDA) and the patent authority (PTO) in the US. The impact of the chiral switch on the surge in use of the racemate and the combinations should be noted. Unfortunately, this chiral switch had to be aborted owing to medical considerations. Recently, the FDA has been alerting the public about the dangers of the Chinese diet pills Chaso (Jianfei) and Chaso Genpi, which contain fenfluramine.

The aborted chiral switch of fluoxetine hydrochloride. Fluoxetine hydrochloride (HCl) — the first selective serotonin-reuptake inhibitor (SSRI)[101,102] and a mainstay medicine for the treatment of depression — was invented, developed and launched in 1988 by Eli Lilly and Company and marketed as Prozac. It proved to be a benchmark and a blockbuster, with worldwide annual sales of US $2.6 billion in 2000 (REF. 60).

Fluoxetine is a racemate of (*R*)-(–)-fluoxetine and (*S*)-(+)-fluoxetine. At the time of the invention, the biochemical and pharmacological activities of each enantiomer were found to be essentially the same[103]. There was little enantiomeric selectivity regarding interactions of fluoxetine with the serotonin-uptake carrier, regardless of the species or pharmacological test. In view of these findings, Eli Lilly did not consider it advantageous

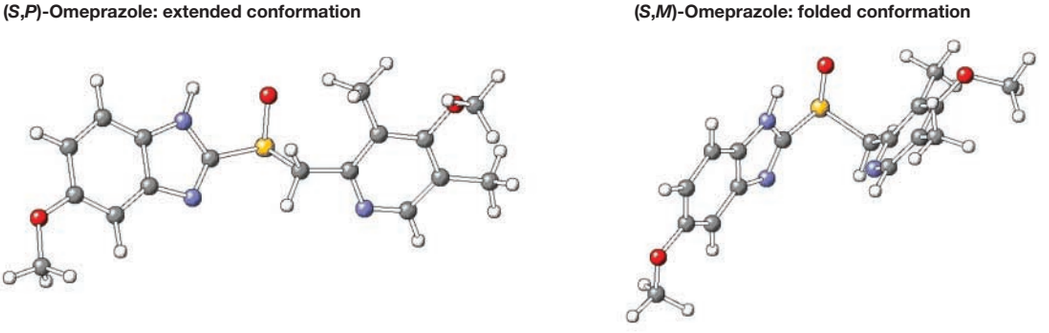


Figure 7 | ***Ab initio* calculated conformations of (*S*,*P*)-omeprazole and (*S*,*M*)-omeprazole.** *Ab initio* density functional theory (DFT)-optimized extended and folded conformations of (*S*,*P*)-omeprazole and (*S*,*M*)-omeprazole, respectively. The colours indicate different types of atom: blue, nitrogen; grey, carbon; red, oxygen; white, hydrogen; yellow, sulphur.

Table 3 | **Chiral switches in the pipeline (2001)**

Racemic drug		Single-enantiomer drug			
Generic name	***Brand name (company)***	***Generic name; stereochemistry***	***Brand name (company)***	***Clinical trials***	***Treatment; indication***
Oxybutynin	Ditropan (Alza)	(*S*)-Oxybutynin	(Sepracor)	Phase III	Reduction of combined micturitions; urge urinary incontinence
Formoterol	Foradil (Novartis)	(*R,R*)-Formoterol	(Sepracor)	Phase III	Bronchodilator; asthma, COPD
Zopiclone	Imovane (Aventis)	Esopiclone; (*S*)-zopiclone	Estorra (Sepracor, Aventis Pharma)	Phase III	Sleep disorders
Acetorphan racecadotril	Tiorfan (Bioprojet)	Ecadotril; (*S*)-acetorphan	Sinorphan (Bioprojet (France); Shionogi, (Japan); Bayer AG)	Phase III	Hypertension and heart failure
Flurbiprofen	Ocufen (Pharmacia), Ansaid (NovoPharma), Froben	(*R*)-Flurbiprofen	Flurizan (Loma Linda University, Myriad Genetics (US), Encore)	Phase III	Colon cancer
Sotalol	Betapace (Schering AG)	(+)-Sotalol	(Bristol-Myers Squibb)	Phase III (terminated, 1995)	Antiarrythmia class III
Fluoxetine HCl	Prozac (Eli Lilly)	(*S*)-Fluoxetine	(Sepracor)	Phase II (on hold since 2001)	Migraine headaches
Fluoxetine HCl	Prozac (Eli Lilly)	(*R*)-Fluoxetine	(Eli Lilly, Sepracor)	Phase II (suspended in 2000)	Antidepressant
Cisapride	Propulsid (Johnson & Johnson)	Ticalopride; (+)-norcisapride (active metabolite of (+)-cisapride)	(Sepracor/Jannssen Pharmaceutica)	Phase II	Irritable bowel syndrome and bulimia
Sibutramine HCl	Meridia (Abbott Laboratories)	Metabolite of (*R*)-sibutramine	(Sepracor)	Phase II	Antidepressant
Sibutramine HCl	Meridia (Abbott Laboratories)	Metabolite of (*S*)-sibutramine	(Sepracor)	Phase II	Sexual dysfunction
Sibutramine HCl	Meridia (Abbott Laboratories)	Metabolite of (*R*)-sibutramine	(Sepracor)	Phase I	ADHD
Doxazosin	Cardura (Pfizer)	(*S*)-Doxazosin	(Sepracor)	Phase I	Benign prostatic hyperplasia
Zopiclone	Imovane (Aventis)	SEP174559	(Sepracor)	Phase I	Anxiety

ADHD, attention deficit hyperactivity disorder; COPD, chronic obstructive pulmonary disease; HCl, hydrochloride.

to seek patents for the single fluoxetine enantiomers as antidepressants. However, Sepracor obtained US Patent 5,589,511 (REF. 104) in December 1996, which claimed (*S*)-(+)-fluoxetine for the treatment of migraine, and US Patent 5,648,396 (REF. 105) in July 1997, which claimed (*R*)-(–)-fluoxetine for the treatment of depression in humans.

Eli Lilly obtained various patents for the single enantiomers of the metabolites of fluoxetine, (*S*)-norfluoxetine[106] and (*R*)-norfluoxetine[107]. Such patents that claim single-enantiomer metabolites of a previously claimed racemic drug might defend against obtaining intellectual property rights in chiral switches of the original racemates.

In December 1998, Eli Lilly and Sepracor announced a license agreement that exclusively allowed Eli Lilly to develop and commercialize (*R*)-fluoxetine globally[108]. (*R*)-Fluoxetine was in Phase II clinical development in the United States as a potential drug for short washout and increased flexibility in treating depression, and (*S*)-fluoxetine has been in Phase II clinical development for potential prevention of migraine. In October 2000, Eli Lilly terminated its licensing and development agreement with Sepracor for (*R*)-fluoxetine, after some patients developed abnormal heart rhythms in Phase II clinical trials. (*R*)-Fluoxetine, at the highest dose tested, caused a small but statistically significant increase in QT_c prolongation (prolongation of the QT interval in the ECG trace). Although Sepracor believed that this cardiac-related side effect was clinically insignificant, development of a lower dose would have delayed the NDA submission by at least two years. Given the risk and timing of the development of (*R*)-fluoxetine, and after an assessment of the competitive environment, Sepracor decided not to pursue the (*R*)-fluoxetine programme at that time.

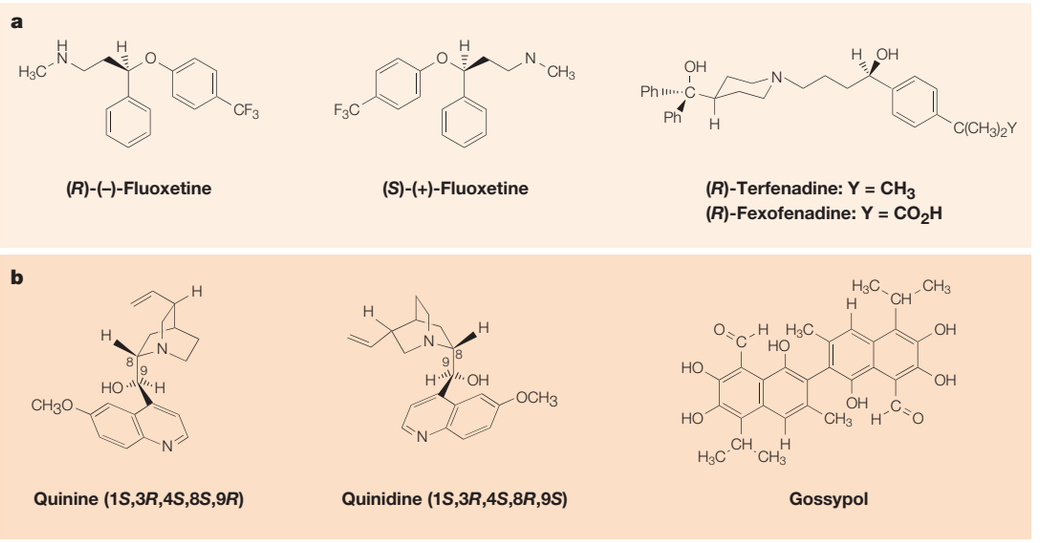


Figure 8 | **Structures of (*R*)-(–)-fluoxetine, (*S*)-(+)-fluoxetine, (*R*)-terfenadine, (*R*)-fexofenadine, quinine, quinidine and gossypol.**

The crucial aspect of timing

It is not unreasonable to surmise that Eli Lilly's decision to abort the chiral switch of fluoxetine HCl to (*R*)-fluoxetine was influenced not only by the obstacles encountered in the clinical trials, but also by the timing factor. For the proprietor of a blockbuster racemic drug, it is imperative that the launching of the single-enantiomer drug takes place before the expiration of the patents of the racemic drug and the incursion of the corresponding generic versions of the drug. The validity of Eli Lilly's patents covering fluoxetine HCl has been the subject of litigation between Eli Lilly and Barr Laboratories, and other generic drug manufacturers, since April 1996. Although this litigation was concerned directly with the racemate, it was also relevant to the chiral switch. When Eli Lilly entered into the licensing and development agreement with Sepracor in December 1998, it expected that Prozac would be protected against the generic versions of the drug until December 2003, when the last of its fluoxetine HCl patents[109] was due to expire. This timetable gave Eli Lilly ample time to develop, obtain FDA approval, launch and market (*R*)-fluoxetine as a second-generation SSRI antidepressant drug, without the intervention of generic-drug manufacturers.

In August 2000, the US Court of Appeals for the Federal Circuit invalidated claim 7 of US Patent 4,626,549 (REF. 109), which dealt with a method of blocking the reuptake of serotonin by neurons in animals by administering fluoxetine HCl, for obviousness-type double patenting (in view of US Patent 4,018,895 (REF. 110)), thereby shortening Prozac's protection by almost three years, to February 2001 (REF. 111) (the expiration date of Eli Lilly's US Patent 4,314,081 (REF. 112)). Although this decision was vacated by the Federal Circuit, in May 2001, the panel issued a second decision that reached the same result, but by a different analysis (double patenting in view of US Patent 4,590,213 (REF. 113)). When Eli Lilly decided, in October 2000, to abort the chiral switch of fluoxetine HCl to (*R*)-fluoxetine, it was evident that it would not be feasible to obtain FDA approval and to launch the single-enantiomer drug before generic versions of Prozac would reach the market. Barr Laboratories launched its generic version of Prozac in August 2001, after the expiry of Eli Lilly's six-month paediatric exclusivity[114]. Eli Lilly's petition to the US Supreme Court for a writ of certiorari to review the judgement of the US Court of Appeals for the Federal Circuit was rejected in January 2002.

There might, however, be an additional interpretation of the chain of events that led to the collapse of the chiral switch to (*R*)-fluoxetine. Eli Lilly might have entered into the licensing agreement with Sepracor to prevent competing companies from developing (*R*)-fluoxetine as a second-generation antidepressant drug. Eli Lilly might then have taken advantage of the difficulties encountered in the Phase II clinical trials to cancel the licensing agreement. At that point, the prospects (if any) of competition for (*R*)-fluoxetine were slim. It remains to be seen whether the chiral switch of fluoxetine HCl to (*S*)-fluoxetine for the treatment of migraine will be pursued successfully.

In conclusion, the chiral switch of fluoxetine HCl highlights the crucial role of timing *vis-à-vis* the intellectual property protection of the racemic drug.

Chiral switches in the pipeline

At present, there are several candidate drugs under development that are derived from chiral switches (TABLE 3). Many of these are in late clinical development (Phase III) and represent the chiral-switch strategy that is articulated here. In addition, some that are earlier in development derive from a refinement of the chiral-switch technique, and come under the broader heading

of the 'strategy of variants', which is also known as the 'improved chemical entities' (ICE) strategy[115]. These are single enantiomers of therapeutically active metabolites that are produced *in vivo* from a racemic drug. Although bridging strategies for such chiral switches of active metabolites require more preclinical studies to establish their pharmacological profiles and to support safety in use, their chemical development can be shortened, and the overall risk of failure reduced. A case in point is the potential variants of fluoxetine HCl (see above), which include, in principle, both the single enantiomers of fluoxetine and the single enantiomers of its active metabolite norfluoxetine. Consider also the application of the variants strategy to the antihistaminic, antiallergic racemic drug terfenadine, which has now been withdrawn (FIG. 8). Its improved racemic active-metabolite variant fexofenadine HCl (Allegra) (FIG. 8) was developed and launched as a non-sedating antihistamine for the treatment of allergic rhinitis. The potential for a chiral switch of fexofenadine still exists.

Concluding comments

In this review, we discuss how the original concept of the chiral switch has developed over the past 15 years. The initial idea that existing racemates would provide an abundant source of new branded or generic single-enantiomer drugs has proved hard to fulfil. However, the chiral switch is, at present, providing a useful option for the owners of existing racemates to achieve line extensions, especially if the switch can be marketed immediately before expiry of the patent on the racemate. This allows patients to be transferred to the new single enantiomer rather than to a generic version of the racemate. The number of chiral switches in the pipeline highlights the popularity of this approach, which is further enhanced when it is seen as part of the strategy of variants, which includes simple enantiomers of active metabolites. However, the attractions of the chiral switch can be viewed as a double-edged sword: whereas advantages, such as reducing the dose compared with the racemate, are of value, the best that can be expected is a halving of the recommended dose, which itself might not be sufficient to justify the switch. Indeed, if the advantage is greater than this, bridging strategies are hard to devise.

Given the emphasis today on the progression of NCEs predominantly as single enantiomers, it might be expected that the chiral-switch idea will soon have run its course, as the number of racemates that are appropriate for line extension dwindles (bearing in mind the proportion of racemates among recently approved NMEs that was discussed above[24,26]). However, the concept might still have its life extended with the investigation of the 'other' enantiomers of natural products and 'nearly natural' drugs that are derived from them. Although the specificity of action of single enantiomers of natural products has been known for more than 100 years, recent findings indicate that the other enantiomer can have separate and useful activities in its own right. Examples include the diastereomeric alkaloids from Cinchona bark — (–)-quinine (1*S*,3*R*,4*S*,8*S*,9*R*)[116] — which is an antimalarial, and its antiarrhythmic quasi-enantiomer[117] (+)-quinidine (1*S*,3*R*,4*S*,8*R*,9*S*)[118] (FIG. 8). A switch from (–)-quinine to (+)-quinine (1*R*,3*S*,4*R*,8*R*,9*S*) would also qualify as a chiral switch.

Another example is the aborted attempt to develop (–)-gossypol as a male contraceptive. Gossypol is a natural yellow pigment obtained from cotton plants, which is present mainly as its (+)-enantiomer[119]. Racemic gossypol (FIG. 8) (isolated from cotton seeds as an acetic-acid solvate) was established as a male antifertility agent in the 1970s in China, an activity that was shown subsequently to reside almost exclusively in the (–)-enantiomer. Although the systemic toxicity and incomplete reversal of its antifertility action prevent use of (–)-gossypol as a male contraceptive[120], it remains of interest as a potential anticancer drug[121,122]. The development of unnatural *ent*-steroids (enantiomers of natural steroids) would also qualify as a chiral switch[123,124].

The synthetic cannabinoid dexanabinol is of particular note. Its (–)-enantiomer HU-210, synthesized in the 1980s as an analogue of Δ^8-tetrahydrocannabinol, is one of the most potent cannabinoids known, and acts through CB_1 and CB_2 receptors. HU-211, the (+)-enantiomer, is devoid of cannabinoid activity but has the typical pharmacological properties of an NMDA (*N*-methyl-D-aspartate) antagonist. This, combined with its antioxidant activity and inhibition of synthesis of tumour-necrosis factor (TNF), indicated that it could be used as a neuroprotective agent. After favourable results in animal models[125], dexanabinol is now in a pivotal Phase III trial in Europe and Israel for traumatic brain injury[126]. Given the range of activities that the other enantiomer of an active simple stereoisomer might have, it seems probable that further useful examples of active drugs will emerge from both natural and synthetic single-enantiomer therapeutic agents.

The vitality of the chiral-switch strategy and the importance of the consideration of loss of exclusivity are highlighted by the recent launch in EU countries of the SSRI antidepressant escitalopram oxalate (Cipralex, Lexapro) (TABLE 1), and its imminent launch in the United States after the granting of FDA approval in August 2002, indicated for the treatment of major depressive disorder[127]. This is occurring despite the fact that sales of the corresponding racemate citalopram hydrobromide (Cipramide, Celexa) are surging. Although the original US Patent for citalopram[128] (published in January 1979, priority date 14 January 1976 (GB Patent 1,526,331)[129]) has expired, citalopram hydrobromide (approved by the FDA in July 1998) has five years of exclusivity (REFS 34,38) as an NME until July 2003, and a further 180 days of pediatric exclusivity[114] until January 2004. Finally, double-switch combinations, such as omeprazole/ibuprofen to esomeprazole/ dexibuprofen, will provide a challenge for intellectual property law and regulatory authorities[9].

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Online links

DATABASES

The following terms in this article are linked online to:

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β_2-adrenoceptor | CB_1 receptor | CB_2 receptor | COX-1 | COX-2 | CYP2C19 | TNF

Medscape DrugInfo: http://www.medscape.com/druginfo
albuterol | amoxycillin | bupivacaine | citalopram hydrobromide | dexmethylphenidate | esomeprazole magnesium | fexofenadine | fluoxetine | ibuprofen | ketoprofen | lansoprazole | levalbuterol | levobupivacaine hydrochloride | levofloxacin | naproxen | omeprazole | pantoprazole | phentermine | rabeprazole | thalidomide

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