Exploiting the Power of Stereochemistry in Drugs: An Overview of Racemic and Enantiopure Drugs

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Abstract: Stereochemistry is one of the essential dimensions in pharmacology as it dictates how enantiomers interact with biological systems. Chirality is very important in drug design. Enantiomers of the same chiral drug can have different pharmacodynamic and/or pharmacokinetic properties. In this context, replacing some existing racemates with single isomers has resulted in improved safety and/or efficacy profile of various racemates. Single enantiomer drug use can potentially lead to simpler and more selective pharmacologic profiles, improved therapeutic indices, simpler pharmacokinetics due to different rates of metabolism of the different enantiomers, decreased drug interactions, and drug companies are increasingly using chiral switching as a marketing strategy. Additionally, due to different pharmacological activity, enantiomers of chiral drugs can differ in toxicity. However, unpredicted toxicity has been reported in some chiral switching cases which has resulted the withdrawal of the enantiomer from the market or a halt in its development. In view of above, before switching to single enantiomer drugs, prescribers should look for evidence from well-conducted clinical trials to prove that the chiral switch is cost-effective and improves the outcomes for patients rather than patents. The U.S. Food and Drug Administration (FDA) have allowed single enantiomers of generic drugs to be patented and marketed under different name. FDA regulations require that all chiral bioactive drug molecules must be isolated and tested for the efficacy and safety, and have to be as pure as possible containing a single pure enantiomer.

Keywords: Chiral drugs, chiral switch, enantiopure drugs, racemic drugs, enantiomers, biocatalysis, pharmacological profile, stereopharmacology.

1. INTRODUCTION

Chiral drugs continue to be a significant force in the global pharmaceutical market as chirality significantly influences a drug's biological and pharmacological properties. Stereochemistry impacts decisions made in the absorption, distribution, metabolism, excretion, and toxicity stages of drug discovery [1]. Stereoselective methods have been employed to study enantioselective metabolic profiling of the active components from Herbal Medicines *in vitro* and *in vivo* in recent years [2]. Chiral drugs make up 40-50% of the market today. The extension of patent protection for drugs manufactured from enantiomers is an important factor that is driving growth of chiral intermediates in pharmaceuticals. For some drugs, only one enantiomer is effective that would, in theory, only require half the effective dose of a 50/50 racemic mixture. In this context, chirality has become a major theme in the design, discovery, development and marketing of new drugs [3-5]. Enantiomers of a chiral drug may work differently in the body [6]. The observed differential antioxidant, but comparable antiinflammatory activities may explain the stereospecific antiischemic activities and different therapeutic time windows of the *trans*- and *cis*-hinokiresinols which possess anti-oxidant, anti-inflammatory and estrogen-like activities. Further, *trans*-hinokiresinol possesses extended profiles in antioxidant activity than *cis*-isomer whereas both hinokiresinols can modulate the inflammatory response [7]. The choice between single stereoisomers (homochiral drugs) and composite chiral drugs (mixtures of stereoisomers) depends upon therapeutic advantages (such as a reduction in xenobiotic load), possible adverse side-effects and development costs. Most illicit drugs are chiral compounds. There is a need for continuous evaluation of existing and new composite chiral drugs. This article focuses on chiral/single enantiopure drugs in relation to pharmacology.

Drugs are classified into achiral, racemic and single-enantiomer (enantiopure) drugs with one-chiral center or multi-chiral centers. An enantiopure drug is a pharmaceutical that is available in one specific purified enantiomeric form. Most commonly, drugs containing a single asymmetric carbon atom exist in two enantiomeric forms, designated as eutomer (the more potent) and distomer (the less potent). Living organisms are made up of chiral, enantiomerically pure compounds. For example, most amino acids in the proteins of all living organisms have the absolute (*S*)-configuration. Enantiomers of drugs often have greatly different affinities at receptor sites, are metabolised at different rates, and have different affinities for tissue and protein binding sites [6]. Despite this knowledge, many drugs are administered as their racemates. “Chiral switch” used to transform an old racemic drug

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into its single active enantiomer can be used to extend the patent life of a drug and assign a new generic name or in developing new blockbusters for Pharma companies. Drug companies also develop ways to purify one enantiomer and provide a medication using only that enantiomer. Single stereoisomer drugs would provide superior therapy by allowing reductions in dosage, reduced variability in metabolism and response, simpler dose-response relationships and improved tolerability [8]. Many enantiopure drugs offer clinical advantages over the racemic forms. One enantiomer of a chiral drug may have a desired beneficial effect while the other may be inactive, or cause serious and undesirable side effects, or sometimes even entirely different effects [9].

2. CHIRALITY

Isomers are compounds with the same molecular formula but different structural formulas. There are two major categories of isomers: constitutional (or structural) isomers and stereoisomers. Constitutional isomers are molecules with the same atomic composition but different bonding arrangements between atoms, as illustrated by the examples of catechol, resorcinol, and hydroquinone (Figure **1**).

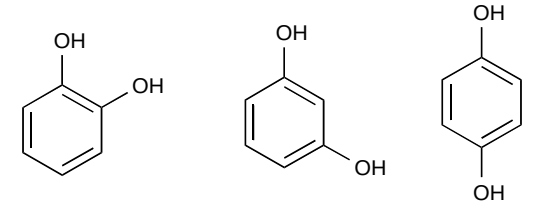


Figure 1: Constitutional isomers.

Stereoisomers are molecules with one or more “chiral” centres that allow the possibility of forms with the same chemical formula but differ in spatial arrangement of atoms. They can be classed as *cis-trans* isomers or optical isomers.

The concept of non-superimposable mirror images i.e. chirality is formally defined as the geometric property of molecule or drug of not being superimposable with its mirror image. The human body is chiral, and hands, feet, and ears are not superimposable. As a hand fits a glove, only the “right” or “left” handed enantiomer may fit a molecular receptor at a drug’s desired site of action. In the (+/-) system, an enantiomer that rotates light clockwise or counter-clockwise is said to be dextrorotatory [d or (+)], or levorotatory [l or (–)], respectively. All living organisms contain almost only ‘left-handed’ amino-acids and ‘right-handed’ sugars. A second difference between enantiomers is their interactions with other chiral substances. For example, enantiomers may have different solubilities in chiral solvents, they may react at different rates in the presence of an optically active reagent or enzyme, and many have different affinities for chiral surfaces and receptors. The D/L system relates the stereochemistry of a molecule to that of a standard reference compound, either the carbohydrate D-glyceraldehyde or the amino acid L-serine. The Cahn, Ingold, and Prelog nomenclature is now employed to assign absolute configuration of the molecular structure of chiral tetrahedral molecules. "R" and "S" refer to the absolute configuration about the "center of asymmetry". In this *R/S* system, based on the specific atoms in the molecule, one configuration is called "rectus" (*R*- for short) and the other is called "sinister" (*S*- for short), from the Latin words for right and left. A racemate is designated as *RS* [10, 11]. The introduction of chirality in penicillin to obtain ampicillin increases its usefulness to kill bacteria that have developed a resistance to penicillin.

The drug methamphetamine has a chiral centre (an asymmetric carbon atom attached to four different substituents) giving rise to two stereoisomers (spatial isomers), known as optical isomers, which are mirror images of each other. On the other hand, aspirin is achiral. The structures of the optical isomers of methamphetamine (chiral) and aspirin (non-chiral) are shown in Figure **2**.

Enantiomers have two non-superimposable mirror-image forms, for example, *S*-Fluoxetine and *R*-Fluoxetine (Figure **3**).

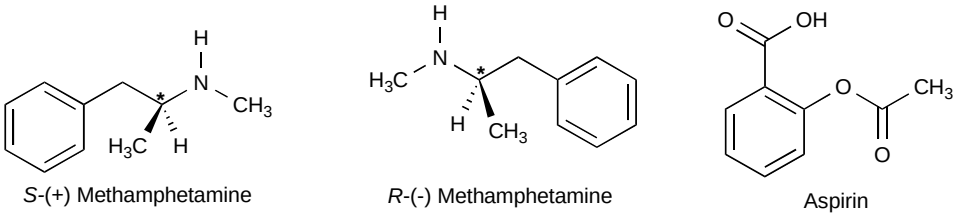


Figure 2: Structure of S-(+)-methamphetamine (chiral), R-(-)-methamphetamine (chiral) and aspirin (achiral).

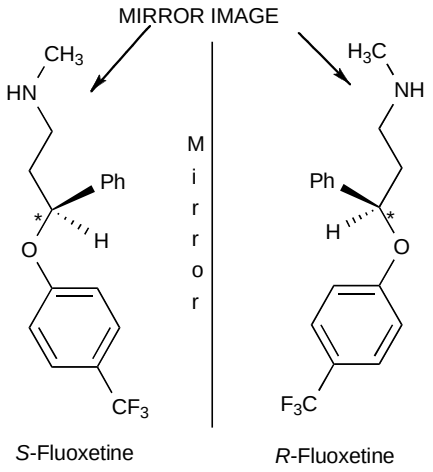


Figure 3: Mirror-image forms: *S*-Fluoxetine and *R*-Fluoxetine.

Most chiral drugs contain one or more chiral centers. Natural compounds are often single enantiomers (e.g. morphine, epinephrine, hyoscine, levothyroxine, levodopa, l-noradrenaline, (-)-brucine) [12, 13]. In contrast, many commercially synthesized drugs are racemic mixtures (e.g. ibuprofen, atenolol, adrenaline, warfarin, fluoxetine, omeprazole) but there is an increasing trend for the pharmaceutical industry to develop and market products containing only the left- or right-handed molecule [14]. Ibuprofen enantiomers are based on carbon stereogenic center**.**

Thalidomide (Figure **4**) is one chiral center hypnotic and anti-nausea drug. The *R*-enantiomer is an effective sedative that relieves anxiety and promotes sleep. However, the *S*-enantiomer may cause teratogen formation. It is important to mention that *S*-thalidomide was shown to be responsible for over 2,000 cases of serious birth defects in children born of women who took it during pregnancy [15].

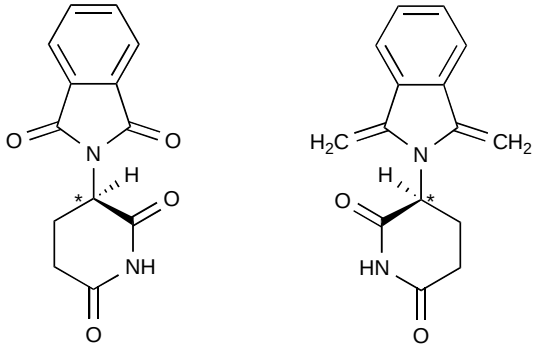


Figure 4: Structure of (*R*)(+)-Thalidomide and (*S*)(-)-Thalidomide.

Sulfur, phosphorus and nitrogen can sometimes form chiral molecules such as omeprazole, cyclophosphamide and methaqualone, respectively [16]. Enantiomers based on phosphorus chiral center may include phosphine, phosphine oxide, phosphinate and phosphonium ion. The antineoplastic agent cyclophosphamide is one example of a compound with a chiral phosphorus moiety [16] (Figure **5**). It is converted in the liver to active forms that have chemotherapeutic activity. The main use of cyclophosphamide is with other chemotherapy agents in the treatment of lymphomas, some forms of brain cancer, leukemia [17] and some solid tumors [18]. Ifosfamide is a nitrogen mustard alkylating agent used in the treatment of cancer (Figure **6**).

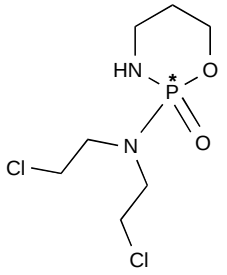


Figure 5: Structure of cyclophosphamide.

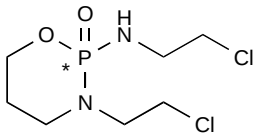


Figure 6: Structure of ifosfamide.

2a. P-Chiral Nucleotide Prodrugs

PSI-7977's (Figure **7**) is a nucleotide strapped on to a phosphoramidate P-chiral prodrug, a "protected" substance which is later converted by the body to the active drug species [19].

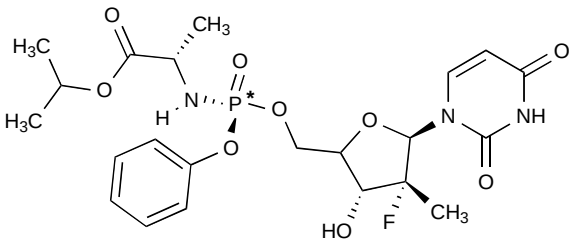


Figure 7: Structure of PSI-7977.

PSI-352938 (Figure **8**) is a novel cyclic phosphate prodrug of β-D-2'-deoxy-2'-α-fluoro-2'-β-C-methylguanosine-5'-monophosphate that has potent activity against hepatitis C virus (HCV) *in vitro* [20, 21].

Enantiomers based on sulfur may include sulfoxide, sulfoximide, sulfinate and sulfoniumion. Enantiomers

based on nitrogen may include amine oxide and ammonium ion. The sulfur atom of the nonsteroidal antiinflammatory sulindac (Figure **9**) bears four different substituents (one being a pair of electrons) and hence is chiral.

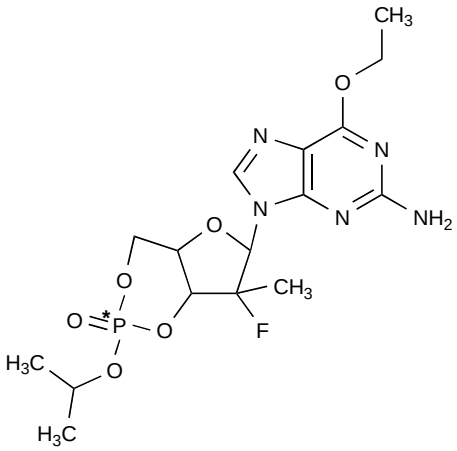


Figure 8: Structure of PSI-352938.

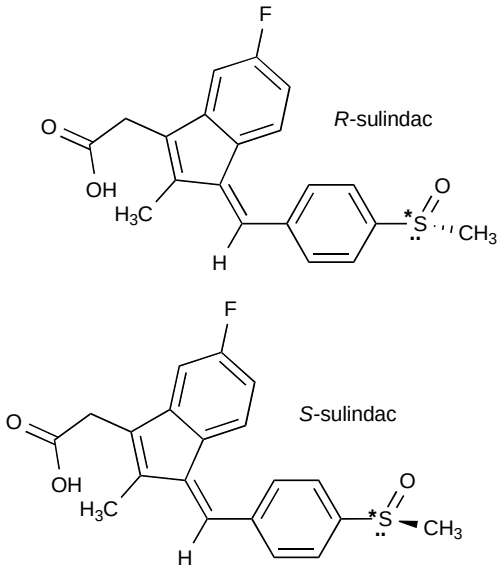


Figure 9: Structure of *S*-sulindac and *R*-sulindac.

Omeprazole (Figure **10**) is an example of a stereogenic sulfur atom. Esomeprazole (*S*-enantiomer of omeprazole) is chiral drug which is used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease and Zollinger-Ellison syndrome.

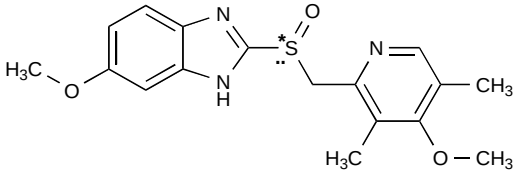


Figure 10: Structure of Esomeprazole.

Armodafinil (Nuvigil) is a stimulant-like enantiopure drug consisting of just the active (−)-(*R*)-enantiomer of the racemic drug Modafinil (Provigil) (Figure **11**). This drug was produced by the pharmaceutical company Cephalon Inc., and was approved by the FDA in 2007 [22].

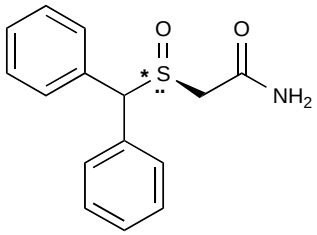


Figure 11: Structure of Armodafinil.

Several terms are commonly used to describe the enantiomer proportions within a given racemic mixture. The *enantiomer ratio* (ER= Enantiomer 1(E_1)/Enantiomer 2(E_2) and *enantiomer fraction* [EF=E_1/(E_1+E_2)] provide similar information. The *enantiomer excess* [*e.e.* =|E_1 - E_2|, where E_1+E_2=1 (or 100%)] is defined as the absolute difference between the mole or weight fraction of each enantiomer, and is commonly expressed as a percentage [23]. A *racemate* (*racemic mixture*) represents 1:1 (equimolar, *e.e.*= 0) mixture of enantiomers. Most illicit drugs are chiral compounds. S(+)-amphetamine has twice as high stimulant activity as R(-)-amphetamine. The verification of enantiomeric ratios for chiral drugs that include amphetamine, methamphetamine, MDMA, MDEA, MDA, ephedrine and pseudoephedrine can provide vital information about patterns of drugs usage and can help in the differentiation between their legal and illicit usage [24].

3. POTENTIAL ADVANTAGES OF ENANTIOPURE DRUGS

Potential advantages of single-enantiomer drugs include: separating unwanted pharmacodynamic side effects from toxic effects in case these reside exclusively in one enantiomer, smaller doses of medication; simpler and more selective pharmacodynamic profile; less complex pharmacokinetic profile; less side-effects because of the elimination of distomers; reduce drug interactions, fewer adverse effects, one form is more prone to adverse drug interactions; reduced metabolic load over the enzymatic system; potential for an improved therapeutic index and less complex relationship between plasma concentration and effect [25-27]. Further, the advantages of enantiopure drugs over

racemic drugs have varied, depending on the case, and the biological effects of single enantiomer drugs over their counterpart racemic drugs still remain unclear in some cases.

3a. Purification and Downstream Processing Strategies

The future of biomanufacturing industry is based on the technology trends in downstream purification processes/bioprocess which are gaining importance as biologic drugs has high potential for future growth because of improvements in cost-effective purification technologies. The goal of the purification strategies is to develop scalable downstream processes for the purification of biopharmaceutical products. Downstream processing is an essential step in the manufacture of pure pharmaceuticals particularly therapeutic protein drug and biopharmaceuticals (e.g. monoclonal antibody), antibiotics, hormones (e.g. insulin and human growth hormone), vaccines, and enzymes used in diagnostics with high yield as priorities generally in marketable quantities [28].

In the downstream phase of manufacturing, the protein product is isolated from the cells that produced it. Special protocols are required to extract intracellular proteins for purification. Usually this involves bursting the cells open to release the protein product, which then has to be purified away from the other components that were inside the cell. In this context, extracellular proteins are easier to isolate. After harvesting the protein product, clarification process separate the protein from cellular debris. Then the protein solution is subjected to a series of chromatography columns where a pure protein product is obtained based on physical and chemical properties such as size, shape or charge (+ or –) of protein. Additional purification steps are required to remove any residual DNA and deactivate any viral particles that may be present.

Stages in downstream processing include: target contaminants, a capture section (removal of insolubles), concentration, capture/initial purification, intermediate purification, final purification and sterilization/formulation. Large-scale chromatography operations continue to occupy a key position in the overall strategy for the downstream processing and purification of protein products for therapeutic use. Affinity, cation-exchange, anion-exchange, ceramic hydroxyapatite, and hydrophobic-interaction membrane chromatography are the main types of chromatography modes used in large-scale bioseparations [29, 30]. Affinity chromatography (a single step purification step) was applied for the purification of monoclonal antibodies [31]. The application of partition designs to a monoclonal antibody purification process was reported [32]. Affinity tags are highly efficient tools for protein purification [33]. A trend from classical purification methods like sucrose gradient centrifugation towards more sophisticated techniques like tangential flow filtration and liquid chromatography is being followed for adenoviruses, adeno-associated viruses or retroviruses [34]. Regarding removal of the host-cell proteins during vaccine purification, the standard purification protocol is based on anion-exchange chromatography followed by cation-exchange chromatography and a final step using hydroxyapatite. Mimetic ligands can be integrated into a purification platform with an affinity capture step that will achieve a high-capacity recovery of the product with excellent removal of host-cell proteins. Integrating tangential flow filtration technology helps overcome the potential bottleneck in capture purification, but it won't replace conventional ultrafiltration for all processes. Disposable technology is increasing in popularity for the final polishing step. Current methodology used in recovery processes for therapeutic monoclonal antibodies was reported [35]. Packed-bed chromatography is the workhorse in the downstream processing of therapeutic monoclonal antibodies. Convective Interaction Media DEAE columns have shown to be a good alternative for the purification of lentiviral vectors which hold great potential as gene delivery vehicles [36]. Cibracon Blue dye resin, a polycyclic anionic ligand, was used to effectively and efficiently separate an IgG4 MAb from host and process impurities following the capture of the MAb on a Protein-A (PA) column [37].

Researchers successfully generated pure biotinylated full-length DENV C protein with an optimized sequential purification protocol involving nickel-nitriloacetic acid affinity chromatography, dialysis, ion exchange-fast protein liquid chromatography and size exclusion chromatography. This purified non-truncated DENV C protein was found suitable for structural and molecular studies [38]. In pharmaceutical industries, downstream processing has an influence on active pharmaceutical ingredients (API) crystals whose properties must be controlled because they influence the end-use properties of the drug. Filter cake washings has been used to remove all the

impurities and to obtain a pure crystalline crystal form of API [39].

3b. Enantiopure Drugs Preparation

The separation of enantiomers is called resolution which is essential in order to ensure the safety and efficiency of chiral compounds. Nowadays, the technologies of resolution and asymmetric synthesis have advanced to the point that the cost of making enantiopure material is not so great, and the FDA is expressing a strong preference that all medicinal drugs are sold in enantiopure form. Drug companies develop ways to obtain one enantiomer and produce a

Table 1: Examples of Chiral Drugs from Various Therapeutic Classes [1, 51-58]

Therapeutic class	Examples
Calcium channel blockers	Verapamil, prenylamine, nimodipine, manipidine, nilvadipine, nicardipine, felodipine, nitrendipine, S-amlodipine besylate, nisoldipine, felodipine, mandipine, gallopamil, diltiazem.
Antiarrhythmics	Propafenone, disopyramide, flecainide, tocainide, maxeletine, encainide, [disopyramide, encainide, flecainide, mexiletine, propafenone and tocainide, verapamil.
beta-blockers	Propranolol, acebutolol, atenolol, alprenolol, betaxolol, carvedilol, meto-prolol, labetalol, pindolol, S-(-)-timolol, S-(-)-pentobutolol, labetatol, nadolol, l-solatol,
NSAIDS	Ibuprofen, ketorolac, naproxen, etodolac ibuprofen, ketoprofen, benoxaprophen, fenprofen, etc.
Tranquilizers : 3-hydroxy-benzodiazepines	oxazepam, lorazepam, temazepam
Antibiotics	Fluoroquinolones, oxacin, moxalactam
Antineoplastics	Cyclophosphamide, iphosphamide
Anticoagulants	Warfarin, acenocoumarol
Muscle relaxants	Methocarbamol, baclofen
Anesthetics	Prilocaine, ketamine, pentobarbital
Antihyperlipidemic	Atorvastatin
Antiemetics	Ondansetron
Antihistamine	Terfenadine, loratadine
Antimalarials	Chloroquine, halofantrine, mefloquine
Proton pump inhibitors	Omeprazole, pantoprazole, lansoprazole
ACE	(S)-(-)-Captopril, Benazepril, (S)-(-)-Enalapril,Imidapril, Valsartan
Opiate analgesics	Methadone, pentazocine
Anaesthetic drugs	Isoflurane, halothane, enflurane(general anaesthetics), etomidate, thiopentone(intravenous anaesthetics), cisatracurium(neuromuscular blocking agents), ropivacaine and levobupivacaine(local anaesthetics), levosimendan, dexmedetomidine, L-cysteine(other agents)
Antiviral	(-)-Carbovir, l-lamivudine
Hypnotics, Sedatives	hexobarbital, secobarbital, mephobarbital, pentobarbital, thiopental, thiohexital
Hormones and endocrinology	Levothyroxine
Respiratory	Albuterol (salbutamol), salmeterol and terbutaline
Cancer therapies	Cytarabine, ifosfamide, (-)-gossypol
Ophthalmic	loteprednol etabonate, Atropine, Bimatoprost (*Ophthalmic* Sol.) betaxoxime, adaprolol, etabonate, and etiprednol dicloacetate
Anti-arthritic	penicillamine
Anti-hypertensive	valsartan, Telmisartan
Anticholinergic	trihexyphenidyl, benztropine, procyclidine, biperiden, ethopropazine, diphenhydramine and orphenadrine

medication using only that enantiomer. Three strategies can be applied to obtain single pure isomers: (i) extraction from plants and animal materials (ii) enantio-selective asymmetric synthesis so that only one isomer is formed in the first place [40] or (iii) making a racemate and finding a method for separating the enantiomers (chiral resolution) [41-43]. Among the variety of enantioseparation methods, classical resolution [44], Simulated Moving Bed technology [45], chiral chromatography and crystallization are the most dominant methods for the recovery of pure enantiomers [46, 47]. The performance of the hybrid SMB-crystallization process was reported for the chiral resolution of mandelic acid as racemic compound [48]. Biocatalysis synthesis routes are also the choice to obtain enantiopure drug. Various enzymes like oxido-reductase, transferase, hydrolase, lyase, isomerase and lipases act on the different prochiral or racemic compounds to yield chirally pure drugs/precursors [49]. The preparation of the enantiopure drug Clopidogrel has been achieved by the employment of the resolution technique called attrition-based deracemisation [50].

4. REPRESENTATIVE CHIRAL DRUGS

Examples of chiral drugs from various therapeutic classes are given in Table **1**.

Annual new drug approvals of racemic and enantiopure drugs have been consistently published by the US Food and Drug Administration [55]. Albendazole is an anthelmintic drug widely used in the treatment of neurocysticercosis, an infection of the brain with *Taenia solium* cysts. Use of (+)-(*R*)-Albendazole sulfoxide (Figure **12**) enantiomer alone may lead to increased efficacy and/or less toxicity compared to albendazole [59].

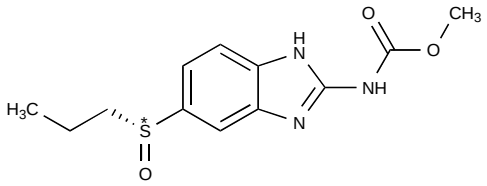


Figure 12: Structure of (*R*)-albendazole *S*-oxide.

Mephedrone (Figure **13**) most probably as a racemic mixture of the *R* and *S* enantiomers is a synthetic psychoactive substance. This drug has been readily available for legal purchase both online and in some stores and has been promoted by aggressive Web-based marketing. Its abuse in many countries, including the United States, is a serious public health concern. Mephedrone has been sold as a 'legal' alternative to 'ecstasy', amphetamines and cocaine. It was first detected in November 2007 and notified *via* the EMCDDA's Early Warning System in March 2008. Evidence of mephedrone use and associated toxicity has been increasing, in 2009 and 2010 [60]. USA temporarily classified mephedrone as illegal, in effect from October 2011. Only little is known about the pharmacology of Mephedrone (4-methylmethcathinone). The *S* form is thought to be more potent than the *R* form, because this applies to cathinone [61]. Mephedrone has a unique pharmacological profile with both abuse liability and neurotoxic potential [62].

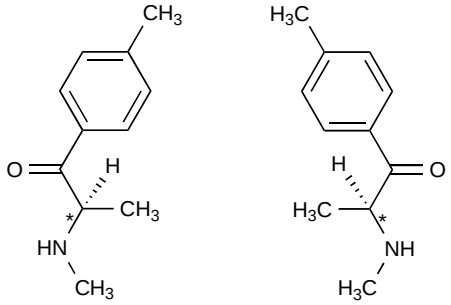


Figure 13: Mephedrone enantiomers structural formulae.

Fenoldopam (Figure **14**) is a dopamine D1 receptor agonist that is used as an antihypertensive agent [63]. Fenoldopam is a racemic mixture of two enantiomers, SK&F R-82526 and SK&F S-82526. The results showed that the renal and systemic vasodilator activities of fenoldopam are properties of the *R*-enantiomer *via* stimulation of postganglionic DA-1 receptors; the *S*-enantiomer is essentially inactive [64].

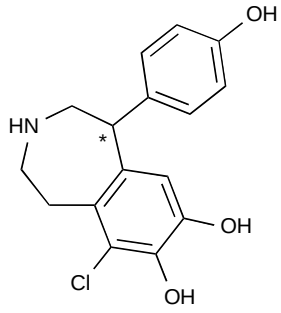


Figure 14: Structure of fenoldopam.

FDA approved *R*(-)-Alogliptin (an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus) (Figure **15**) by Takeda Pharmaceuticals America, Inc. in 2013.

R-Tafluprost (Zioptan) by Merck used for management of ocular hypertension was approved by FDA in 2012 (Figure **16**).

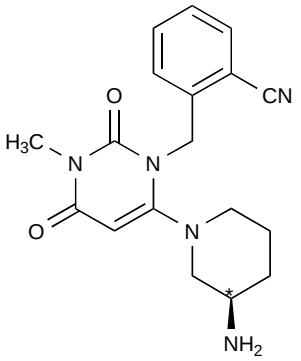


Figure 15: Structure of *R*(-)-Alogliptin.

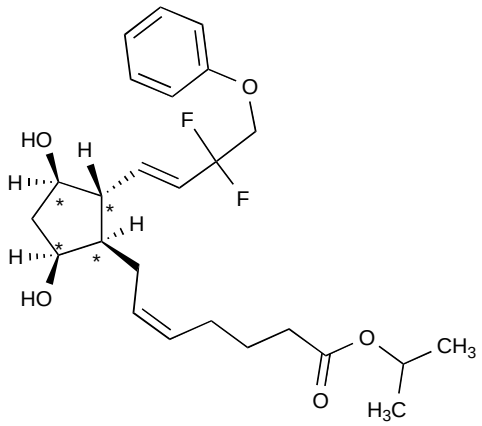


Figure 16: Structure of *R*-Tafluprost.

Ingenol mebutate (Picato) by Leo Pharma was approved in 2012 by FDA for treatment of actinic keratosis. FDA had approved Johnson & Johnson new anti-tuberculosis drug Bedaquiline (Sirturo, TMC207 or R207910) (Figure 17) in December 2012. This is a new treatment for multidrug-resistant tuberculosis that can be used as an alternative when other drugs fail [65]. Further study is desired to assess relative activity of both enantiomers.

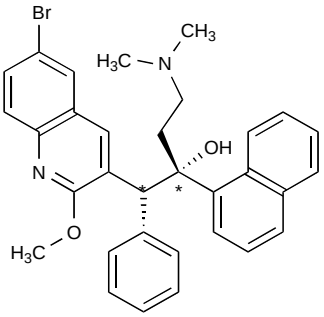
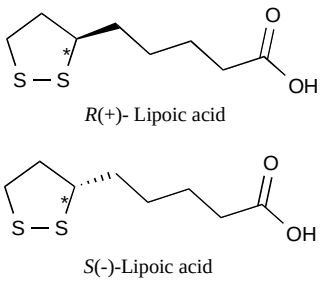


Figure 17: Structure of racemic bedaquiline.

Thioctic acid (Figure **18**), also known as alpha-lipoic acid (1,2-dithiolane-3-pentanoic acid), is a naturally occurring antioxidant that neutralizes free radicals in the fatty and watery regions of cells.



R(+)- Lipoic acid

S(-)-Lipoic acid

Figure 18: Structure of lipoic acid enantiomers.

Racemic alpha-lipoic acid (50/50 mixture of the *R*(+)-(natural) and *S*(-)-(unnatural) enantiomers) is the most widely available commercial form of lipoic acid. Both the reduced and oxidized forms of the compound possess antioxidant ability. The pyruvate dehydrogenase (PDH Complex) is a multi-enzyme complex that plays a vital role as a key regulatory step in the central pathways of energy metabolism in the mitochondria. The natural cofactor of the complex is the (+)-thioctic acid. Moreover, (-)-thioctic acid acts either as a poor substrate or as an inhibitor of (+)-thioctic acid when it interacts with 2-oxoacid dehydrogenase multienzyme complexes. Both (+)- and (-)-thioctic acid are reduced intracellularly *via* two enzymatic pathways. (+)-Thioctic acid demonstrated more pronounced effect and the lack of activity of (-)-thioctic acid may have practical therapeutic implications worthy of being investigated in further preclinical and clinical studies [66]. It is unclear whether the two enantiomeric forms (R & S) of lipoic acid (LA) share similar pharmacological activity and the exact cellular targets of LA are not well identified.

Mefloquine (Figure **19**) is currently manufactured and sold as a racemate of the (*R*,*S*)- and (*S*,*R*)-enantiomers by Hoffman-LaRoche, a Swiss pharmaceutical company. Essentially, it is two drugs in one. (+)-Mefloquine is more effective in treating malaria, and the (–)-Mefloquine specifically binds to adenosine receptors in the central nervous system, which may explain some of its psychotropic effects [67].

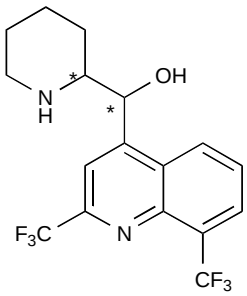


Figure 19: Structure of mefloquine.

Table 2: Name, Number and Type of Chiral Atoms of Some Representative Chiral Drugs

Drug	Number and nature of chiral atoms	Activity	Drug	Number and nature of chiral atoms	Activity
Armodafinil	1(C)	for the treatment of narcolepsy and shift work sleep disorder, and as an adjunctive treatment for obstructive sleep apnea.	(*S*)-Clopidogrel	1(C)	used for treatment of ischemic strokes, heart attacks, atherosclerosis
Darifenacin	1(C)	the treatment of urinary incontinence and overactive bladder	Sitagliptin	1(C)	treatment of type 2 diabetes
Penicillamine	1(C)	used to treat Wilson's disease	Albuterol	1(C)	used to treat asthma
Levofloxacin	1(C)	a broad spectrum antibiotic	Desvenlafaxine	1(C)	an antidepressant of the serotonin-norepinephrine reuptake inhibitor class
Etodolac	1(C)	NSAID	Pindolol	1(C)	beta blocker
R-Selegiline	1(C)	used to help control the symptoms of Parkinson's disease	Levonorgestrel	1(C)	used to prevent pregnancy after unprotected sexual intercourse
Pegaptanib	1(C)	for neovascular age-related macular degeneration	Fesoterodine fumarate dextrorotary enantiomer	1(C)	to treat overactive bladder syndrome
Montelukast	1(C)	used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies	Valacyclovir	1(C)	an antiviral drug used in the management of herpes simplex, herpes zoster (shingles), and herpes B) is manufactured as one stereoisomer
Ramelteon	1(C)	the treatment of insomnia	Ivabradine	1(C)	used for the treatment of angina
Darunavir	1(C)	used to treat HIV infection Only the R-enantiomer is biologically active	Rivastigmine tartrate	1(C)	a reversible cholinesterase inhibitor
Moxifloxacin	2(C)	a broad-spectrum antibiotic	Arformotero	2(C)	used for the treatment of chronic obstructive pulmonary disease
Ephedrine	2(C)	used as a stimulant, decongestant and bronchodilator	Labetalol	2(C)	used to treat high blood pressure
Sertraline	2(C)	antidepressant	(2R,2'R)-(+)-threo-methylphenidate	2(C)	a psychostimulant drug
Cephalexin	3(C)	treats infections caused by bacteria	dextromethorphan	3(C)	an antitussive (cough suppressant)
Telbivudine	3(C)	used in the treatment of hepatitis B infection	Fosamprenavir	3(C)	a pro-drug of the protease inhibitor and antiretroviral drug amprenavir
Nadolol	3(C)	used in the treatment of high blood pressure	Moxalactam	3(C)	Antimicrobial agent
Penicillin G, Penicillin V	3(C)	β-lactam antibiotics	Tamilflu	3(C)	Antiviral drug
Xenical	4(C)	To treat obesity	Prostaglandin E1	4(C)	used in the treatment of erectile dysfunction

(Table 2). Continued.

Drug	Number and nature of chiral atoms	Activity	Drug	Number and nature of chiral atoms	Activity
Oxycodone	4(C)	relief of moderate to severe pain	Amoxicillin	4(C)	used to treat infections caused by bacteria
Indinavir sulphate	5(C)	treat HIV infectionas a single agent or in combination with other anti-HIV drugs	Cocaine	5(C)	acts as a serotonin–norepinephrine–dopamine reuptake inhibitor
Chlortetracycline	5(C)	Antibiotic, applicable for bacterial conjunctivitis	Tetracycline	5(C)	an antibiotic used to treat bacterial infections
Norethynodred	5(C)	anabolic steroid used in the treatment of functional uterine bleeding and endometriosis	Morphine	5(C)	a potent opiate analgesic drug
Ertapenem sodium	6(C)	a first-line treat-ment for cephalosporin-resistant gram-negative infections	Norethindrone	6(C)	used in some combined oral contraceptive pills
Ticagrelor	6(C)	a platelet aggregation inhibitor	telaprevir	6(C)	a hepatitis C virus
Ixabepilone	7(C)	used for the treatment of metastatic or locally advanced breast cancer)	Methenolone	7(C)	anabolic steroid
Artemisinin	7(C)	used to treat multi-drug resistant strains of falciparum malaria	vinblastine	7(C)	anticancer agent
Lovastatin	8(C)	a cholesterol- lowering drug	Vincristine	9(C)	alkaloid
Vecuronium bromide	10(C)	muscle relaxant	erythronolide B	10(C)	biosynthetic precursor of all of the Erythromycins
Taxol	11(C)	Anti cancer	(+)-Discodermolide	13(C)	a novel chemotherapeutic agen
Rapamycin.	15(C)	A novel immunosuppressant	Streptomycin	15(C)	an antibiotic (antimycobacterial)
Thiostrepton	17(C)	an antibiotic	Erythromycin A	18(C)	an antibiotic used to treat a wide variety of bacterial infections.
Esomeprazole	1(S)	proton pump inhibitor	Pantoprazole	1(S)	proton pump inhibitor
Dexrabeprazole	1(S)	an antiulcer drug) asymmetric sulfur in its chemical structure	*R*-Sulindac	1(S)	NSAID
(*R*)-albendazole *S*-oxide	1(S)	an anthelmintic drug widely used in the treatment of neurocysticercosis	flosequinan	1(S)	a peripheral vasodilator
Cyclophosphamide	1(P)	Chemotherapeutic agent	Ifosfamide	1(P)	used in the treatment of cancer
Cisatracurium besylate	2(N) 2(C)	neuromuscular-blocking drug	heroin	5(C) 1(N)	used to treat severe pain,

The stereospecificity of *S*-Ropivacaine decreases cardiotoxicity [68].

The name, nature, number of chiral atoms and activity of some other representative chiral drugs (racemate and enantiopure) are given in Table **2**.

5. PHARMACOLOGICAL DIFFERENCES BETWEEN TWO ENANTIOMERS OF A CHIRAL DRUG

The human body is a highly complex chiral environment. After chiral drugs affect the body, two enantiomers bound to macromolecular show differences in aspect of mechanism and integration, thereby, resulting in the stereoselectivity characteristics of the chiral drug and differences in pharmacology. The pharmacodynamic properties of drugs describe their interactions with selective targets on the body, including transport proteins, tissue and blood plasma proteins, enzymes and receptors, steroids, dose-response phenomena, and mechanisms of therapeutic and toxic action [69]. Pharmacokinetics (described as what the body does to a drug) refers to the time course of the various events that a drug and its metabolites undergo in the body, such as absorption, distribution, metabolism and excretion. There are multiple examples of varied receptor types with chiral dependence. However, the magnitude of the differences between a pair of enantiomers in their pharmacokinetic parameters tends to be relatively modest in comparison to their pharmacodynamic properties [70]. Stereoselective metabolism of drugs is most commonly the major causative factor to stereoselectivity in pharmacokinetics as metabolizing enzymes often exhibit a preference for one enantiomer of a chiral drug over the other [71, 72]. The structural characteristics of enzymes dictate the enantiomeric discrimination related with the metabolism of chiral drugs [73]. The clinical pharmacology of chiral drugs is based on understanding the nature of pharmacodynamics and pharmacokinetics important differences for the optimization of pharmacotherapy [74].

Pharmacological activity of drugs depends mainly on their interaction with drug targets, such as proteins (receptors, enzymes), nucleic acids (DNA and RNA) and biomembranes (phospholipids and glycolipids). Drugs interact with receptors by three types of chemical forces: covalent, electrostatic, and hydrophobic. Drugs must interact with a chiral receptor in a cell. One enantiomer “fits” the receptor and evokes a specific response. Its mirror image doesn’t fit the same receptor, making it ineffective; or if it “fits” another receptor, it can induce a totally different response. The binding of nateglinide enantiomers with human plasma, human serum albumin and bovine serum albumin indicated opposite stereo-selectivity

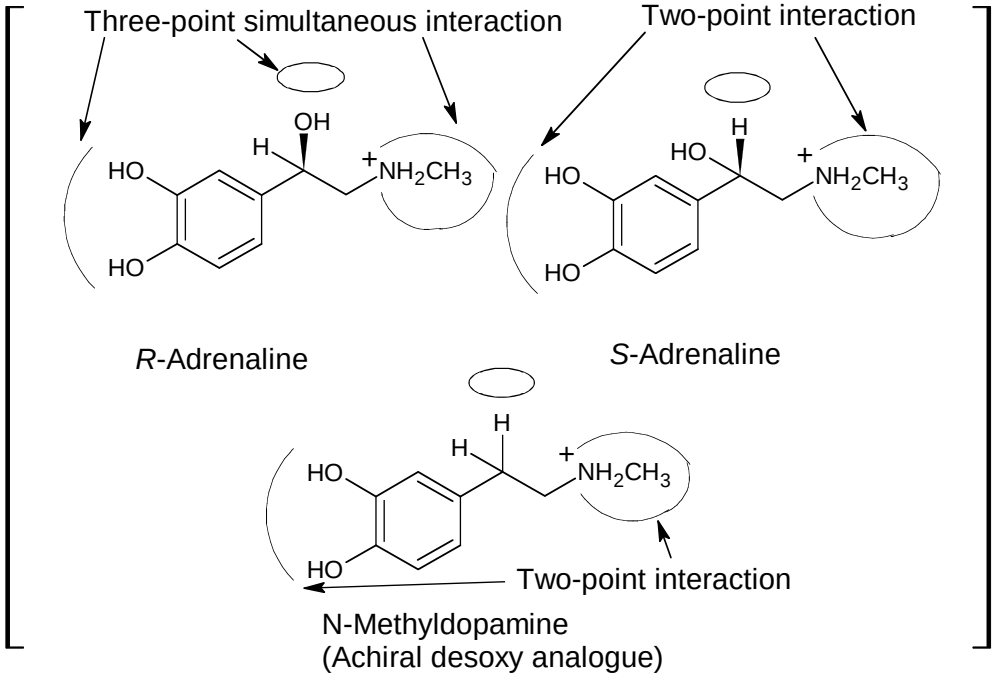


Figure 20: Only in *R*-adrenaline, three functionalities involved in desired drug-receptor interaction, i) methylamino group, ii) catechol ring system, iii) secondary alcohol are appropriately placed.

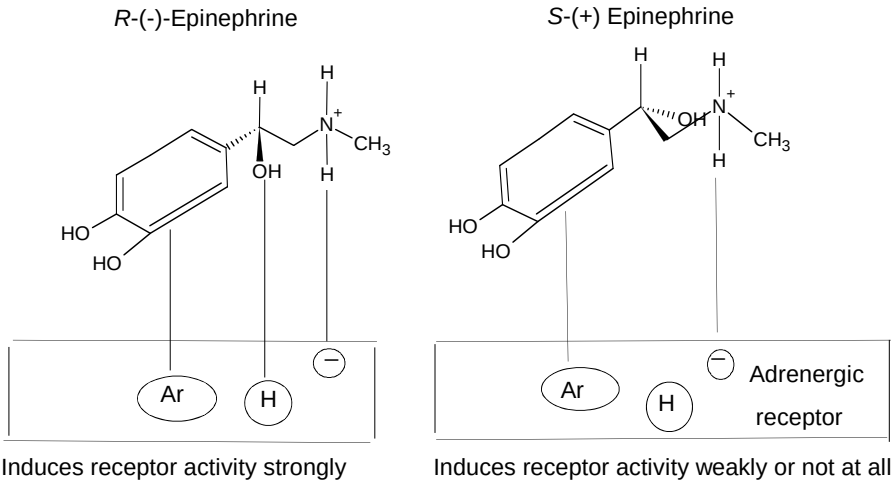


Figure 21: Drug-receptor binding.

between bovine serum albumin and human serum albumin while stereo-selectivity was identical between human serum albumin and human plasma [75]. Based on Easson-Stedman Principle with three-point binding model [76], only one enantiomer binds to enzyme & desired reaction occurs (Figures **20** and **21**).

Mesecar and Koshland model reveals that a fourth location, either a direction requirement or an additional binding site, is essential to distinguish between a pair of enantiomers. Further, that the three-point model is only applicable if the assumption is made that the substrate can approach a planar surface from one direction [77]. (*S*)- Naproxen is common over-the-counter pain reliever and it binds to the enzyme cyclooxygenase and inhibits its action in the synthesis of prostaglandins. Only the (*S*)-naproxen isomer will bind to and inhibit the cyclooxygenase enzyme to decrease prostaglandin production. Decreasing prostaglandin production at the site of injury decreases pain and inflammation [78]. Naproxen (Figure **22**) is a promising lead compound for novel antivirals against influenza A virus that targets the nucleoprotein in its RNA binding groove [79]; however, it is not known whether both or only one enantiomers is responsible for this reaction.

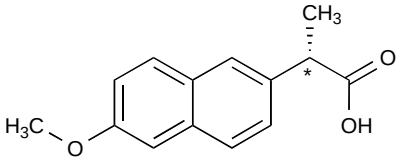


Figure 22: Structure of *S* (+)-Naproxen.

(*R*)-Naproxen does not inhibit the cyclooxygenase enzyme and it is toxic to the liver. The structural difference is due to the different arrangement of groups (H-, H_3C-, HOOC-)-surrounding the central carbon stereocenter. In specific cases, both mirror-image forms of a particular compound can bind at the same time in the same site of an enzyme. The arrangement of the molecules within the binding site was found quite different when both bind together. This could lead to cooperative effects, producing either an enhanced or diminished response relative to the individual enantiomers [80]. The hyptonic effect of zopiclone and eszopiclone results from their interaction with the γ–aminobutyric acid receptors. This leads to an increase in chloride transmission that subsequently depresses the cental nervous system, slowing brain activity, and promoting sedation. Eszopiclone's affinity for this receptor complex has been shown to be twice that of its racemic parent, while the leavorotatory isomer affinity for these receptors is negligible [81].

Langmuir monolayer technique is a powerful method to discriminate between local anaesthetic (*R*)- and (*S*)-enantiomer articaine interaction with model membranes [82]. The above mentioned variations in behaviour of both enantiomers may guide to differences in pharmacology, pharmacokinetics, therapeutic effect, efficacy, and toxicity [83-86]. Drug therapies illustrating the clinical importance of chirality and stereochemistry have been reported [87-89]. The difference between enantiomers can mean a difference between therapeutic and adverse effects, as well as in beneficial pharmacological effect and potency [90-92]. Validated bioanalytical methods should always be used for measurement of individual enantiomers in bioequivalence studies when the enantiomers exhibit different pharmacodynamic characteristics [93, 94].

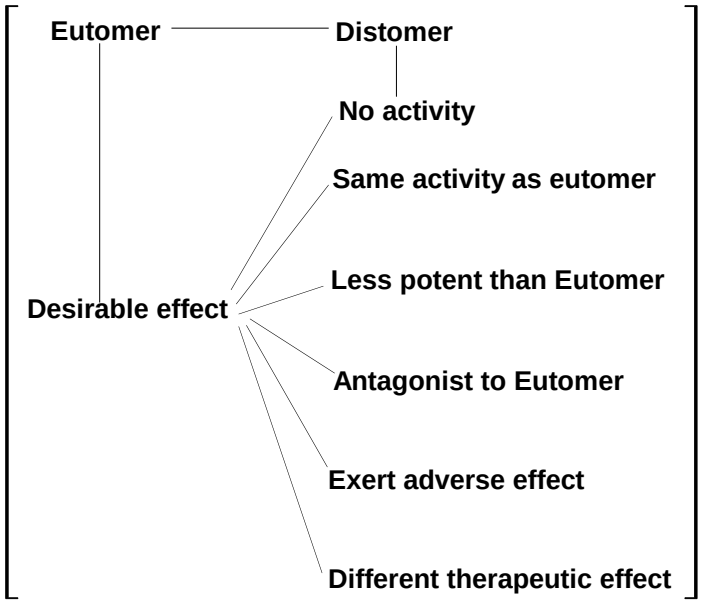


Figure 23: Enantiomeric interaction possibilities of eutomer and distomer.

5.1. Pharmacodynamic Implications of the Concept of Chirality in Drug Activity

Racemic drugs activity can be divided into different groups (Figure **23**, Tables **3-7**). The majority of racemic pharmaceuticals have one major bioactive enantiomer (eutomer) and a less bioactive enantiomer (distomer) [11].

Examination of the pharmacodynamic properties of a pair of enantiomers may yield a number of possible scenarios:

i). Examples where one enantiomer is 'active', while the other enantiomer is "inactive.

This category includes a number of cardiovascular drugs, agents widely used for the treatment of hypertension, heart failure, arrhythmias, and other diseases (Table **3**).

ii). Examples where one isomer is more potent than the other (Table **4**).

iii). Examples of beneficial effects in one enantiomer whilst the other enantiomer has adverse activity (Table **5**).

iv). Where enantiomers have entirely different therapeutic possibilities (Table **6**).

v) The beneficial effects reside in one enantiomer, the other enantiomer having antagonistic activity (Table **7**).

vi). Both enantiomers having equal therapeutic potency/equally biologically active (Table **8**).

Enantiomers of antiarrhythmic drugs (flecainide, mexiletine, tocainide, propafenone) and antimalarials (mefloquine, halofantrine, enpiroline) have small or no differences in their potency. Only some racemic drugs that could belong to this group include cyclophosphamide (antineoplastic), flecainide (antiarrhythmic), fluoxetine (antidepressant) [90] and prometazine (antihistamine) [114]. However, R, R and S, S Tramadol enantiomers contribute to the similar analgesic pharmacological activity *via* different mechanisms.

5.2. Racemic Drugs with Chiral Inversion

Chiral inversion can take place in two ways, unidirectional and bidirectional conversion. Examples of racemic drugs with chiral inversion include oxazepam, lorazepam, temazepam, omeprazole, levobupivacaine, ibuprofen, ketoprofen, fenoprofen, benoxaprophen [115]. 2-Arylpropionic acids (ibuprofen, ketoprofen, fenoprofen, benoxaprophen, etc. and collectively called as profens) undergo unidirectional metabolic bioconversion of the inactive *R*-enantiomer into the active *S*-enantiomer [116, 117]. Unidirectional inversion of several D-amino acids such as DNNA, D-leucine, D-methionine, D-phenylalanine and D-3,4-dihydroxyphenylalanine (D-DOPA) has been documented in mammals [118]. 3-Hydroxy-benzodiazepines (oxazepam, lorazepam, temazepam)

Table 3: Examples where One Enantiomer is Active While Another is (Almost) Inactive [95-100]

Racemic drug (Application)	Active enantiomer	Racemic drug (Application)	Active enantiomer
Atenolol (a cardioselective β-adrenergic blocker)	(S)-(-)-Atenolol	Cetirizine (antihistaminic profile)	(*R)*-(-)-Cetirizine levocetirizine
Ofloxacin (antibacterial activity)	(S)-(-)-Levofloxacin	Fenoldopam (an antihypertensive agent)	*R*-(-)- Fenoldopam
Citalopram (antidepressant)	Escitalopram {(*S*)-(-)-citalopram{	Fluvastatin (used to treat hypercholesterolemia)	(3R,5S)-(+)-Fluvastatin
Methyldopa (used against hypertension)	L-isomer of alpha-methyldopa (S)-(-)-Methyldopa	Methadone (used as a pain reliever and opioid agonist)	*R*-(-)-Methadone
Propranolol (used to treat hypertension, anxiety and panic)	(*S*)-(-)-Propranolol	Oxprenolol (used for the treatment of angina pectoris, abnormal heart rhythms and high blood pressure)	(*S*)-(-)-Oxprenolol
Hexobarbital (Hypnotics or sedative used in psychiatric treatment)	(*S*)-(+)-Hexobarbital (*S*)- hexobarbital was metabolized 1.5 times faster than its (*R*)-*enantiomer*,	Ketamine (Anesthetic)	S-(+)-Ketamine
S-Clopidogrel (a potent antiplatelet drug)	(S)-(+)-Clopidogrel	Fesoterodine	*(R)*-(+)- Fesoterodine
Oxybutynin	(*R*)-Oxybutynin	Benzetimide,(an antimuscarinic drug)	(S)-(+)-Dexetimide
Betaxolol (used for reducing elevated intraocular pressure)	*S*-(-)-Betaxolol	Praziquantel	(*R*) –(–)-Praziquantel

Table 4: Examples of More Potent Enantiomer [11, 101-104]

Racemic drug	More potent enantiomer (eutomer)	Racemic drug	More potent enantiomer
Citalopram	(S)-(+)-Citalopram	Albendazole sulfoxide	(+)-(*R*)- Albendazole sulfoxide
Ondansetron (Anti-emetics)	R-(+)-Ondansetron	Verapamil	(S)-(-)-Verapamil S
(±)-threo- methylphenidate (used in the treatment of attention deficit-hyperactivity disorder)	d-threo-(R,R)-methylphenidate (2R,2'R)-(+)-threo-methylphenidate	Pantoprazole (used to treat erosive esophagitis and other conditions involving excess stomach acid)	-(-)-Pantoprazole
Omeprazole (used in the treatment of dyspepsia, peptic ulcer disease)	Esomeprazole [(*S*)-(-)-Omeprazole]	Ibuprofen (used for pain relief, fever reduction)	(*S*)-(+)-Ibuprofen
Captopril (used for the treatment of hypertension and congestive heart failure)	*S*-(-)-Captopril l-Isomer	Methadone (used as a pain reliever and opioid agonist)	*R*-(-)-Methadone
Warfarin (oral anticoagulant drug)	*S*-Warfarin	Tenatoprazole (used for the treatment of acid-related diseases)	(*S*)-(-)-Tenatoprazole

(Table 4). Continued.

Racemic drug	More potent enantiomer (eutomer)	Racemic drug	More potent enantiomer
(+) S,S –Ethambutol (used to treat tuberculosis)	(+) S,S -Ethambutol	Venlafaxine (used to treat major depressive disorder, anxiety, and panic disorder)	R-(-)-Venlafaxine is relatively more potent than the S-enantiomer with regard to inhibition of noradrenaline reuptake ; the S-(+)-enantiomer is more potent regarding inhibition of serotonin reuptake.
racemic XK469	R(+)XK469 The R-isomer of a synthetic quinoxaline phenoxypropionic acid derivative with proapoptotic and antiproliferative activities	Carvedilol	(*S*)-(–) Carvedilol a drug that interacts with adrenoceptors, is 100 times more potent as beta receptor blocker than (*R*)-(+) isomer
Metoprolol	S-Metoprolol provision of the beta-1 blocker component only, avoiding the beta-2 blocking component	Atenolol	S-Atenolol: provision of the active beta-1 blocker component only
Amlodipine	S-amlodipine provision of the active CCB component only	Timolol (decreases intraocular pressure and is used in the treatment of glaucoma)	S(–) timolol
oxazepam	S(+)-oxazepam	secobarbital	S(-)-secobarbital
Thiopentone	S(-)-thiopentone	trihexyphenidyl	R-trihexyphenidyl
“Ecstacy”, also known as MDMA	(S)-(+)-Ecstacy	Propranolol	S-(-)-Propranolol
Timolol	(S)-(-)-Timolol	Penbutolol	(*S*)-(-)-Penbutolol
Valsartan (calcium channel antagosists)	(S)-( )-Valsartan	cyclophosphamide	R-(+)-Cyclophosphamide
Eszopiclone (for the treatment of insomnia)	*S*(+)-Zopiclone	Ketoprofen (anti-inflammatory effects)	*R*-Ketoprofen
Methacholine (a parasympathomimetic drug)	*S*(+)- Methacholine	Felodipine (an oral calcium channel blocker)	*S*-(-)-Felodipine
Propranolol (β-adrenoceptor antagonist)	*S*(-)-Propranolol	Ofloxacin (antibacterial activity)	(*S*)-(-)-Ofloxacin
Repaglinide (the treatment of type II diabetes)	*S*(+)-Repaglinide	Etodolac (NSAID)	S-(+)-Etodolac

Table 5: One Enantiomer Exhibits Beneficial Effects Whilst the other Enantiomer has Adverse Activity [105-107]

Racemic drug	Beneficial effect enantiomer	Adverse activity enantiomer
Ketamine	S(+)-Ketamine is an active anesthetic and analgesic	Hallucination and agitation is associated with the *R*(-)-distomer
Penicillamine	*S*-Penicillamine used to treat arthritis	*R*- Penicillamine is toxic
Naproxen	(*S*)-Naproxen	*R*-naproxen causes liver poisoning with no analgesic effect.
Ethambutol	(*S,S*)-enantiomer is tuberculostatic	(*R,R*)-enantiomer causes blindness
Thalidomide	(*R*)-enantiomer of thalidomide is effective against morning sickness	(*S*)-enantiomer is teratogenic,
Citalopram	Citalopram is a selective serotonin reuptake inhibitor and the *S*-enantiomer is responsible for this effect	The *R*-Citalopram is therapeutically inactive, but displays other effects or side-effects

Table 6: Enantiomers have Entirely Different Therapeutic Possibilities [108-111]

Drug	(+)-Enantiomer	(-)-Enantiomer
Sotalol	(-)-Sotalol β-adrenoceptor blocker	(+)-Sotalol antiarrythmic agent
Methylamphetamine	*S*-Methylamphetamine is the most potent in terms of CNS stimulant activity.	R-methylamphetamine is a decongestant'
Venlafaxine	*R* potent inhibitor of serotonin and noradrenaline reuptake	*S*-enantiomer is more selective in inhibiting serotonin reuptake
Sibutramine	*R*-Sibutramine metabolite is under evaluation for the treatment of depression	*S*-Sibutramine metabolite may be useful for the treatment of erectile and ejaculatory dysfunction.
Methorphan	(+)-Methorphan is an over the counter cough suppressant, as well as dissociative hallucinogen	(-)-Methorphan is a controlled narcotic that was never clinically developed.
Methorphan	Cough suppressant and has no analgesic or narcotic properties	an opioid narcotic and a Schedule II drug [56].
Tetramisole	R-(+)-Dexamisole antidepressant	S-(-)-levamisole nematocidal immunostimulant
Penicillamine	Antirheumatic (Wilson's disease)	Neurotoxic
3-Methoxy cyproheptadiene	(+)-3-Methoxy cyproheptadiene antiserotonin activity	(-)-3-Methoxy cyproheptadiene anticholinergic activity
Indacrinone	S-(+)-Indacrinone uricosuric	R-(-) Indacrinone natriuretic
Venlafaxine	inhibitor of serotonin and noradrenaline reuptake	inhibiting serotonin reuptake.
Levodopa	Antiparkinsonian	Agranuloctosic
Estrone	Sexual hormone	Inactive
Barbiturates	Excitation	Sedation
Dobutamine	Vasodilatation	Positive inotropic/ vasoconstriction
Fluoxetine	Selective serotonin reuptake inhibitor	Minimal effect
Pentazocine	Anxiety	Analgesia, respiratory depress-ion
Propoxyphene	Analgesia	Antitussive
Propanolol	Suppress ventricular arrhythmia without β-adrenergic blockade	Active β-adrenergic blocker
Thyroxine	Inactive	Thyroxemic effect
Verpamil	Minimal effect	Negative dromotropic; negative inotropic and chronotropic effect
Acenocoumarol	Anticoagulant	Minimal effect
Thalidomide	Mutagenic	Sedative-hypnotic teratogenic
Albuterol	Proinflammatory effect	Bronchodilator
Morphine	Minimal effect	Strong analgesic
10-Hydroxy-carbazepine	Antiepileptic	Minimal effect
Methadone	Minimal effect	Strong analgesic
Warfarin	Weak anticoagulant	Anticoagulant
Racemorphane	(+)-N-Methyl-3-methoxy morphinane analgesic	(-)-N-Methyl-3-methoxy morphinane antitussive
methylphenylpropyl barbituric acid	R-anaesthetic	S-convulsant.
Ritalin	(R,R)-Ritalin used to treat Attention Deficit Disorder	(S,S)-Ritalin an antidepressant

Table 7: Beneficial Effects Reside in One Enantiomer, the other Enantiomer having Antagonistic Activity [112, 113]

Racemic drug	Agonist (Beneficial activity enantiomer)	Antagonistic (opposite activity enantiomer)
Albuterol (bronchodilators are used in the treatment of asthma)	bronchodilator activity resides in *R*-Albuterol	*S*-Albuterol
Lipoic acid	*R*-Lipoic acid	S- Lipoic acid
Indacrinone	*R*- Indacrinone (diuretic)	*S*- Indacrinone (uricosuric)
Picenadol (opioid analgesic)	(+)-(3*S*,4*R*) enantiomer	(-)-(3*R*, 4*S*) enantiomer
Dobutamine (activities against α-adrenoceptors)	(–)-Dobutamine	(+)-Dobutamine
Beclofen	(*R*)-Beclofen	(S)-Beclofen
Propafenone	(*S*)-propafenone	(*R*)-Propafenone
Picenadol (agonist-antagonist analgesic and act at the opiate receptors)	*R* (+)-Picenadol	*S*(-)-Picenadol

Table 8: Examples of both Enantiomers having Equal Therapeutic Potency/Equally Biologically Active

Cyclophosphamide (Antineoplastic)	Flecainide (Antiarrhythmic)
Fluoxetine (Antidepressant)	Promethazine (Antihistamine)
Ibuprofen (used for pain relief, fever reduction, and swelling)	Propafenone (Antiarrhythmic)
Fexofenadine (Antihistaminic effects)	SCH00013 (cardiotonic agent)
Omeprazole (used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease)	Lansoprazole (used to treat and prevent stomach and intestinal ulcers)
Tramadol (used to treat moderate to moderately severe pain)	Carvedilol (Alpha-adrenergic blocking activity)
Nateglinide (an oral antidiabetic agent)	

and thalidomide undergo bidirectional chiral inversion whereby the *R* and *S* enantiomers undergo racemisation [11].

6. PHARMACOKINETIC DIFFERENCES BETWEEN ENANTIOMERS

The processes of absorption, distribution and metabolism are crucial determinants of drug action and can assume equal relevance to the actual biological effect of the drug at its receptor site. Stereoselectivity in pharmacokinetics may be characterized by a measurable difference between enantiomers in a pharmacokinetic parameter. Pharmacokinetic parameters can be divided into different levels of organisation and that the hybrid character of parameters increases with the level of organization that they represent [119].

i) Parameters with the highest degree of hybrid character describe the pharmacokinetic behavior of a drug in the whole body (for example systemic clearance, volume of distribution and half-life);

ii) At the organ level, pharmacokinetic parameters represent the combined effects of stereoselectivity in each of their component parameters within an organ (for example hepatic metabolic clearance, renal clearance);

iii) At the molecular level, fraction unbound in plasma, intrinsic metabolic formation clearance reflects the selectivity of an endogenous macromolecule for the enantiomers of a chiral drug molecule [120-122]. Indeed, many studies have demonstrated that stereoisomers of a chiral drug often exhibited pronounced differences in their pharmacokinetic and metabolic profiles both quantitatively and qualitatively [16, 123]. In addition to differences in potency and other pharmacodynamic properties, most members of enantiomeric pairs commonly differ also in their pharmacokinetic profiles [124, 125]. A literature review indicates that stereoselective pharmacokinetics, rather than stereoselective pharmacological activity, is the main cause of differences in clinical efficacy between pure enantiomer and racemic proton-pump inhibitors. The preferred enantiomer of proton-pump inhibitors is not always in the same absolute configuration, i.e., *S*-form is for omeprazole, pantoprazole and tenatoprazole whereas *R*-form is for lansoprazole and rabeprazole [126].

Some specific examples are given below:

i) The bioavailability of (*R*)-verapamil is more than double that of (*S*)-verapamil due to reduced hepatic first-pass metabolism [127].

ii) The volume of distribution of (*R*)-methadone is double that of (*S*)-methadone due to lower plasma binding and increased tissue binding [127].

iii) The clearance of (*R*)-fluoxetine is about four times greater than (*S*)-fluoxetine due to a higher rate of enzyme metabolism [127].

iv) The renal clearance of (*R*)-pindolol is 25% less than (*S*)-pindolol due to reduced renal tubular secretion [127].

These differences in clearance and volume of distribution translate into differences in half-life. For example the half-life of (*S*)-fluoxetine is one quarter that of (*R*)-fluoxetine. In addition, these pharmacokinetic properties can be modified in a stereoselective manner by disease, genetics, ethnicity, age and other drugs. Finally, the enantiomers of some drugs such as warfarin can be metabolised by different enzymes.

v) The *R*-enantiomer of modafinil, which is used in the drug Armodafinil to treat sleepiness, has been proven to last longer than its counterpart *S*-enantiomer [126].

vi) Both renal and total clearance and volume of distribution of (*S*)-(+)-disopyramide were significantly less than those of the *R* enantiomer after administration of the racemate **.**

vii) A superior pharmacokinetic profile, i.e., higher maximal plasma concentrations (C_{max}) and area under the curve, was observed with (*R*)-(+)-rabeprazole compared to its (*S*)-(-)-enantiomer [128].

viii) (*S*)-(-)-omeprazole is cleared more slowly and has an improved oral bioavailability (81%-98% *vs* 35%-65%), leading to the greater inhibition of gastric acid secretion compared to omeprazole.

ix) Both enantiomers of lansoprazole possess equal potency. CYP2C19 genotype influences the disposition of (*S*)-(-)-lansoprazole to a greater extent than the (*R*)-(+)-enantiomer, resulting in less interpatient variability in clearance with (*R*)-(+)-lansoprazole compared to lansoprazole. Therefore, the use of (*R*)-(+)-lansoprazole alone would be highly desirable for clinical application [128].

xi) L-dopa is rapidly absorbed from the gut by an active process whereas D-Dopa is slowly [129].

xii) In the case of indacrinone which is used in the treatment of hypertension and congestive heart failure, the free fractions are 0.9% and 0.3% for the (*R*)- and (*S*)-enantiomer respectively [130].

xii) The (*S*)-enantiomer of barbiturate hexobarbital has an elimination half-life which is three times longer than that of the (*R*)-enantiomer as a result of metabolic clearance [131].

xiii) Renal clearance of [*S*-(-)-pindolol L-pindolol(a synthetic beta-adrenergic receptor blocking agent used to treat high blood pressure and to prevent angina) is faster than that of *R*-(+) – Pindolol [132].

The potential for discrimination between enantiomers at each of these stages is therefore important and highlights the need for stereospecific drug assays [11]. The clinical picture is more complicated. For example, the results of studies of enantiopure escitalopram versus racemic citalopram

have mixed results [133, 134]. Armodafinil (Nuvigil), the *R*-enantiomer of modafinil (Provigil) stays in the body longer than the *S*-enantiomer, so theoretically, it may work better or longer than racemic modafinil. However, there are no data yet on whether armodafinil actually works better than racemic modafinil. Right-handed" thalidomide stops nausea and vomiting, while "left-handed" thalidomide causes severe birth defects [135].

7. TOXICOLOGY

Many drugs can often be associated with complex pharmacokinetics and observed toxicities compared to drugs that are administrated as a single enantiomer. The various stereochemical aspects associated with the metabolism and toxicity of chiral drugs has been reported [136]. Enantiomers of chiral drugs can differ in toxicity due to different pharmacological activity. Many chiral drugs can often be associated with complex pharmacokinetics and observed toxicities compared to drugs that are administrated as a single enantiomer [137-139]. In some cases, chiral switching has been of no benefit. For example, the clinical development of (*R*)-fluoxetine for depression (based on a more acceptable half-life and less propensity for significant drug-drug interactions) was stopped because of a small but statistically significant prolongation of the QT interval with high doses. Dilevalol was thought to have advantages over labetalol, but was removed from the Japanese market because of hepatotoxicity [127].

In addition to variable pharmacodynamic properties, numerous studies have shown that the individual enantiomers of a chiral drug often display stereoselectivity in pharmacokinetics, toxicity, and drug disposition, particularly in the area of drug metabolism. Stereochemical aspects associated with the metabolism and toxicity of chiral drugs have been reported [140]. Enantiomers may result in stereoselective toxicity due to pharmacodynamic and pharmacokinetic differences between enantiomers. In toxicology, the different toxic effects of chiral drugs can reside either in one enantiomer only or in both ones. The toxicological properties in a pair of enantiomers can be identical or entirely different. They can reside in the pharmacologically active enantiomer or in the inactive one [11]. Dopa or dihydroxy-3,4 phenylalanine is a precursor of dopamine that is effective in the treatment of Parkinson disease. Dopa was used under racemic form: d,l- dopa, but owing to the grave toxicity (agranulocytosis) of d-isomer, therefore, only levoratory form called l-Dopa is actually used in therapeutics. Tetramisole is a nematocide, first used under racemic form. Because of numerous side-effects (vertigo, headache, vomiting, abdominal pain) mainly due to d-isomer, therefore, only l-isomer called levamisole is now used in medicine. L-(*R*)-carnitine is primarily used in the treatment of valproate toxicity. Neither the D-isomer nor the racemate should be antidotally administered [138]. Pharmacology and toxicological effects can coexist in the same enantiomer or both. In this context, clinical superiority of escitalopram, *R*-albuterol and cyclophosphamide still need to be demonstrated [140]. The *R*-(-) fenoprofen enantiomer is metabolically inverted to the *S*-(+) fenoprofen enantiomer in the liver and severe hepatic disease should alter the percentage of chiral inversion obtained for *R*-(-) fenoprofen. Researchers studied the chiral inversion of *R*-(-) fenoprofen in cats with toxic hepatic disease induced by carbon tethrachloride and the percentage of chiral inversion in animals with toxic hepatic disease was 90.5±21.1 and the difference with healthy animals was not statistically significant [141]. Interconversions occurred after the oral and i.v. administration of *R*- flosequinan enantiomers and S-flosequinan enantiomers [142].

8. ENANTIOMERS USE IN HOMEOPATHY

Modulation of toxicity of enantiomers provides possibility for therapeutics, since they target multiple points in biochemical pathways. Inhibition of the excitotoxic neurotransmitter L-glutamic acid with homeopathic preparations of D-glutamic acid indicates the latter may be of use for amelioration of symptoms of disturbances of mood. Similarly, homeopathic preparation of (+)-nicotine may be of use for inhibition of effects of nicotine in tobacco [143]. ISOMOOD™ Homeopathic medicine contains a homeopathic formulation of D-Glutamic acid which may gently inhibit the toxic effects of a brain chemical called L-Glutamic acid, which on a molecular level is an exact mirror image of D-Glutamic acid. L-Glutamic acid is known to be involved in feelings of anxiety, nervous tension and mood swings and thus helps with anxiety treatment and stress reduction.

The toxic effects of an optical isomer may be counteracted or reversed by the administration of a potentized preparation of one of its enantiomer. Researchers concluded that toxicity of intraperitoneal injection of (-)-U50488 hydrochloride may be inhibited by administration of a mixture of potencies of its enantiomer [144]. Researchers concluded that the toxicity of intraperitoneal (-)-propranolol HCl, may be counteracted by administration of a potency of its

enantiomer, in ICR conventional mice which have survived preceding intraperitoneal Rometar injection, and pre-dosing with (+)-propranolol HCl homeopathic potency [145].

9. PHARMACOGENETIC ASPECTS

Pharmacogenomics refers to the general study of all of the many different genes that determine drug behaviour. Besides environmental factors, genetic factors regulate the fate of drugs in the organism. Some polymorphic enzymes such as some cytochrome P-450 isozymes display stereoselectivity toward chiral substrates or in the formation of chiral metabolites from achiral parent compounds. The pharmacogenetics of metabolism of psychotropic drugs based mainly on the study of the polymorphic enzymes CYP2D6 and CYP2C19, and the knowledge on the pharmacology, metabolism, pharmacokinetics, and pharmacogenetics of antidepressants, antipsychotics, and methadone has been reported [146].

Genetic differences between people contribute to inter-individual differences in the response to many commonly used drugs. Pharmacogenetics primarily uses genetic variation to identify subgroups of patients who may respond differently to a certain medication and comprises of genetic studies on both the pharmacokinetics and pharmacodynamics of treatment response [147]. The pharmacogenetics of drug metabolising enzymes and particular the cytochrome P450 (CYP) enzymes has been in the focus for almost 40 years. Early experiments with debrisoquine and nortriptyline documented that patients fall into different categories: poor, intermediate, extensive and ultra-rapid metabolizers. A recent study confirmed an association between CYP2D6-allele/plasma level concentrations of venlafaxine, although it did not find any such association for desvenlafaxine (an antidepre ssant of the serotonin-norepinephrine reuptake inhibitor). Desvenlafaxine is a synthetic form of the isolated major active metabolite of venlafaxine [148]. The genetically variable CYP450-mediated metabolism of a number of serotonin-active drugs that are often implicated in cases of serotonin toxicity, to assess the impact of pharmacogenetics on drug metabolism, response, interactions and adverse effects has been reported [149] A patient's response to a chiral drug is influenced by their genome, so pharmacogenetics could be used to determine drug sensitivity.

Clinically available, warfarin consists of a racemic mixture of two active optical isomers, (*R*)- and (*S*)-isoforms, and their pharmacokinetic and pharmacodynamic properties differ considerably, because the (*S*)-enantiomer is three times more potent than the (*R*)-enantiomer. There is a considerable controversy about the clinical use of genotyping before starting the anticoagulant therapy [150]. The current evidence base for pharmacogenetics in relation to drug-metabolizing enzymes was reported [151]. The relationship between pharmacokinetics and pharmacogenetics for venlafaxine and citalopram, with emphasis on enantiomeric drug disposition in different biomatrices has been reported and the CYP2D enzymes display a significant impact on the stereoselective metabolism of citalopram and venlafaxine drugs [152, 153].

10. REGULATORY AFFAIRS IN SINGLE ENANTIOMERIC DRUGS

The enantiomers of a chiral drug show different pharmacokinetic and pharmacodynamic profiles. Satisfactory standards of quality, safety, and efficacy need to be demonstrated for medicines containing chiral active ingredients before they can receive an authorization to place them on the market [154]. Regulatory authorities implied guidelines that clearly state that the development of an enantiopure drug should be preferred, while it also has to be demonstrated that the developed drug is indeed enantiopure. The United States Food and Drug Administration (FDA) issued guidelines and policies in 1992 concerning the development of stereoisomeric drugs (enentiopure and racemic drugs) [155]. FDA urged the pharmaceutical industries to evaluate enantiopure drugs alongside racemic drugs as new candidates for the future. Further, world scientific and regulatories bodies (European Union, Canada, Japan) released guidelines for the development and manufacture of enantiopure drugs [156]. The regulatory review for marketing approval (safety and efficacy) and for patenting (proprietary rights) is independent, and differs country by country. Guidelines on the investigation of chiral active substances were issued by a commission of the European countries in 1994 and by Canadian Government in 2000. The importance of evaluating the behaviour of stereoisomers was further highlighted in FDA regulatory document in 2005. Based on case-to case study, the U.S. Food and Drug Administration (FDA) allowed single enantiomers of certain drugs to be marketed under a different name than the racemic mixture. Also case-by-case, the United States Patent Office has granted patents for single enantiomers of certain drugs [157].

Chiral Separation and Patent Laws

The field of chiral separations has had a bearing on the outcome regarding the "inventiveness" of chiral drug molecules when patent law is applied [158]. Overall, all regulatory guidance recommends the investigators to identify the chirality of principle ingredient, manufacturing process, stability testing and labelling criteria of the final drug. Pharma companies have needed to make decisions whether to develop and seek protection of either the racemic mixture or the single enantiomers, or whether to pursue a chiral switching route instead by seeking to first patent the racemic drug, and then years down the road seeking to extend a drug product's life cycle by subsequently patenting the single enantiomer form of the drug [159]. On a case-by-case basis, the FDA has allowed single enantiomers of certain drugs to be marketed under a different name than the racemic mixture.

11. CONCLUSION AND PERSPECTIVES

There is no requirement from any regulatory authorities for marketing single isomers. However, to reduce the risk of distomer in our body, the pharmaceutical industries are looking for the development of optically pure enantiomers as chiral molecules are huge business for the pharmaceutical industry. In this direction, the increasing availability of single-enantiomer drugs promises to offer clinicians with safer, better-tolerated, and more efficacious medications for treating patients. Relatively little is known about stereochemistry concerning route of administration, dose, formulation, drug interactions, age gender, disease and genetics. The enantiomers of drugs often behave differently from each other in bio-environment and the two enantiomers of a racemate can differ in their pharmacokinetic /pharmacodynamic and efficacy/ safety profiles**.** Pharmacokinetics and pharmacodynamics of chiral drugs with particular reference to bioequivalence determination should be further investigated. Continuous reevaluation should enable reintroduction of old racemates as single-enantiomer products with cleaner pharmacological profiles.

Medications consisting of a single purified enantiomers include levonorgestrel/ethinyl estradiol, Escitalopram, Dextroamphetamine, Levofloxacin, Esomeprazole, Levetiracetam, Levonorgestrel, Eszopiclone, Dexmethylphenidate, Levometham-phetamine, Dexmedetomidine, Armodafinil, Dextrorphan, Levosalbutamol, Levorphanol, Dexlansoprazole, Levoamphetamine, Esmirtazapine, Arformoterol, Levacetylmethadol, Dexfenfluramine, Levosulpiride, Esmirtazapine, Levomethorphan, Dexrazoxane, Eslicarbazepine acetate, Levobupi-vacaine, Dexbrompheniramine, Dexketoprofen, D-Deprenyl, Esreboxetine, Dextromethorphan, Levopropylhexedrine, Levoverbenone, Levobetaxolol. In some cases, where the beneficial medical effects emerge exclusively or primarily from one enantiomer, creating a single enantiomer version of the drug can provide effective treatment with fewer side effects. These safer alternatives include levosalbutamol, *S*-ketamine, levobupivacaine, *S*-zopiclone, levocetirizine, *S*-amlodipine, *S*-atenolol, *S*-metoprolol, *S*-omeprazole, *S*-pantoprazole and *R*-ondansetron, levofloxacin, dexketoprofen [160].

Chiral switches overcome patent protection. However, chiral switching can lead to unexpected toxicity in spite of advantages such as lower therapeutic doses, more safety margin, less inter-individual variability, less drug interaction, and few side effects. The higher eudismic ratio is considered as an important tool in drug discovery and drug designing and manipulation of enantiomeric composition from 1:1 ratio found in the racemate by increasing the content of active enantiomer should be further exploited to obtain improved therapeutic profile in a resulting mixture. Further, racemates should continue to be reevaluated for pharmacodynamics, pharmacokinetics, toxicological properties except in cases of rapid isomerisation within the body, and reintroduced as an enantiopure drug with improved therapeutic benefits. While pursuing scientific investigations (pharmacokinetic, pharmcodynamic, genetics or toxicologic) on handed-drugs, it is mandatory that the aspect under study be viewed from both sides of the mirror. At present, there are not many enantiopure drugs which show considerable clinical value over the racemic versions. But the enantioselective investigations viz. pK and pD studies on racemic therapeutics provide valuable information. Some examples of this approach are the development of the single enantiomer esomeprazole from the racemate omeprazole and the single enantiomer escitalopram from the racemate citalopram. Better among racemates include fluoxetine, dobutamine than enantiopure drug. In some cases (e.g., ibuprofen and thalidomide), the enantiomers interconvert or racemize *in vivo*. This means that preparing a pure enantiomer for medication is largely pointless.

The practicing physician should be familiar with the basic characteristics of chiral pharmaceutical. When both a single enantiomer and a racemic formulation of a drug are available, the information from clinical trials and clinical experience should be used to decide whether go for chiral switching or not. Choice of stereoisomeric form must be justified on scientific grounds. Factors influencing chiral inversion need further investigations before chiral switching.

Overall, the ultimate goal of drug development and pharmaceutical manufacturers should be to obtain superior quality medicines to make drug therapy more effective, specific and safer for the benefit of mankind. There is an urgent need for pharmacists to educate themselves regarding various issues pertaining to drug chirality and pharmacological consequences. Pharmacists should provide updated information on chiral drugs especially racemic forms to healthcare professionals to enable them to find an optimal treatment and achieve a right therapeutic control. In addition, physicians need to reassess the rationality of existing racemates and also determine the clinical value of recent enantiopure introductions.

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