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A Review: Stereochemical consideration and eudismic ratio in chiral drug development

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Abstract: Over the past fifteen to twenty years, the stereochemistry is gaining prime importance in pharmaceutical practice. As a result of advancement in chemical technologies associated with the synthesis, separation, identification and analysis of single enantiomer present in racemic compound, several chiral drugs are presented as single enantiomer for approval to regulatory authorities. Rather to introduce a racemic compound, a single enantiomer always have better selectivity on receptor resulting in superior therapeutics action with less metabolic load and less side effects. The enzymes or amino acids or binding sites have long been recognized to be stereoselective which is considered in chiral drug development. Each enantiomer interacts differently with the receptor, elicits the response differently and potency of enantiomer depends on the eudismic ratio or eudismic index or stereospecific index of the compound. Therefore Eudismic ratio is also an important tool in chiral drug designing. The issues related to eudismic ratio are presented in this review article and it facilitates us for single enantiomer development.

Keywords: Enatiomer, Eudismic ratio, Stereoselectivity, Chiral drug, Eutomer, Distomer

Introduction:

The origin of the discovery and development of stereochemistry in pharmaceuticals dates back to the late 1850's, when Pasteur reported the different destruction rates of *dextro* and *levo* isomers of ammonium tartrate by the mold *Penicillium glaucum*. In his observations, Pasteur emphasized: "Most natural organic products, the vital products of life, are asymmetric and possess such asymmetry that they are not superimposable on their images." For some grounds, this knowledge of racemic organic compounds and racemisation seemed to be avoided until the question of racemic compounds was raised by Ariens in the late 1980's. He asked the question" why we in some cases have to give doses to the patient where half of the content has no effect or the opposite effect?" After this revival of stereochemistry, the regulatory authorities defined more strict requirements on drug discovery and chiral compounds. Besides the ethical reasons, the therapeutic benefit (efficacy and safety) and, in several instances, extensions of the life cycle of drugs have been impetus for developing single enantiomers [1].

The biological activity (both pharmacological and toxicological) of the enantiomers is considered as the tool of advance research because of the different activities shown by R-enantiomer and S-enantiomer of the racemic drug in biological system. Due to different activities, importance of single enantiomers utility is appreciated and several methods are adopting to resolve the racemic compounds into optically pure entity [2].

Therefore, single enantiomer always has advantage over the racemate. Our body can recognize only one enantiomer which in result produces therapeutic effect; other may have undesirable effects/ no effects/ toxic effects. This interest in drug stereochemistry has resulted from the considerable advances in the synthesis, analysis, separation and formulation of chiral compounds, together with an increased appreciation of the potential significance of the differential biological properties of the enantiomers of the chiral drugs. For some therapeutics, single-enantiomer formulations can provide greater selectivities for their biological targets, improved therapeutic indices, and/or better pharmacokinetics than a mixture of enantiomers [3].

In some cases, both a mixture of enantiomers and a single-enantiomer formulation of a drug will be available simultaneously. In these cases, familiarity with stereochemistry and its pharmacologic implications will aid the practicing physician to provide optimal pharmacotherapy to his or her patients. As a result of these advances in the

technology and the potential benefits of the single enantiomer, drug stereochemistry became an issue for the pharmaceutical industry and the regulatory authorities [4]. This article reviews illustrate stereochemistry and enantiomers, emphasizing the potential biological and pharmacologic differences between the two optically active enantiomers of a drug, and highlights the significance of eudismic ratio of racemic mixtures in chiral drug discovery and development.

Market ov erview on single enantiomer necessity

Approximately 50% of marketed drugs are chiral, and of these approximately 50% are mixtures of enantiomers rather than single enantiomers.[5] Single–enantiomer drug sales show a continuous growth worldwide and many of the top selling drugs are marketed as single enantiomers as depicted in table 1.

In 2001, of the $ 410 billion in worldwide sales of formulated pharmaceutical products $ 147 billion belongs to single-enantiomer drugs. The worldwide market for dosage forms of single-enantiomer drugs was $123 billion in 2000, increasing by 7.2%, from $115 billion in 1999. Geographically, the U.S. is the biggest consumer of enantiomeric fine chemicals, contributing to a total North American share of $3.98 billion, making up 60% of the total. European and Asian consumption of enantiomeric fine chemicals is not expected to grow as fast, with the North American share rising to 66.9% of the market in 2007, equivalent to $10.7 billion. Some drug companies have patented and developed a racemic drug, with the intention of patenting and developing a single enantiomer later. When the patent on the racemate expires, the company can undercut generic competition by launching the single-enantiomer. AstraZeneca, for instance, has developed esomeprazole (Nexium), a single enantiomer version of its $6 billion anti-ulcer drug omeprazole (Prilosec), which came off patent in 2002. shows the growth of single enantiomer annually upto 2005 and still the growth continuously increasing [6-8].

Worldwide, the market for chiral fine chemicals sold as single enantiomers was $6.63 billion in 2000 and is expected to grow at a rate of 13.2% annually, reaching $16.0 billion in 2007. The drug industry is the driving engine for this strong growth, accounting for 81.2% of the total, equal to an overall worth of $5.38 billion, in the year 2000. The remaining $1.25 billion is divided among such uses as agricultural chemicals. electronic chemicals, flavors and fragrances. The numbers look even more impressive when considered as the sale of single-enantiomer compounds made into the pharmaceutical formulations that people actually consume [1]. The business of developing single isomer drugs came about, because the chemical production methods used for pharmaceuticals often produced racemic mixtures of two enantiomers. In 1960s the case of thalidomide, it was shown that one enantiomer was responsible for efficacy and another for side effects or teratogenicity resulted into deformalities in new born babies.

Single enantiomer drugs are increasingly popular for the practicing physician. The manufacturers are keen to provide the optically pure drugs to avoid the undesirable side effects of the distomer. The decision to use a single enantiomer versus a mixture of enantiomers of a particular drug should be made on the basis of the data from clinical trials and clinical experience. The use of single enantiomer drugs 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, and decreased drug interactions. Single enantiomer formulations of (S)-albuterol, a selective alpha-2 adrenergic receptor agonist used in

Table 1: Worldwide sales of single-enantiomer pharmaceutical final products

Therapeutic category	2000 sales (in $ billions)	2004 sales (in $ billions)	2005 sales (in $ billions)	% Annual growth(2000-2005)
Cardiovascular	27.65	34.033	36.196	6
Antibiotics and antifungals	25.942	32.305	34.298	6
Cancer therapies	12.201	21.358	27.172	17
Hematology	11.989	20.199	22.439	13
Hormones and endocrinology	15.228	20.608	22.355	8
Central nervous System	9.322	17.106	18.551	15
Respiratory	6.505	12.827	14.708	18
Antiviral	5.89	11.654	14.683	20
Gastrointestinal	4.171	11.647	13.476	26
Ophthalmic	2.265	3.063	3.416	9
Dermatological	1.272	1.486	1.561	4
Vaccines	1.427	2.45	3.1	17
Others	7.128	10.4	13.268	13
Total	130.991	199.66	225.223	11

the treatment of asthma and (S)-omeprazole, a proton pump inhibitor for the treatment of gastrointestinal reflux, have been shown good therapeutic efficacy which is superior to racemic formulations in clinical trials. [9]

In 1992, the Food Drug Adminisrtration in USA published a policy regarding single enationtiomers. The policy was also followed by Europian guideline in 1993. There is no absolute requirement from any of the major regulatory authorities for the development of single enantiomer drugs and decision regarding the stereoisomeric form i.e. single enantiomer or racemic mixture to be developed is left to the developer [10]. However, the decision taken requires specific justification based on quality, safety and efficacy, together with the risk-benefit ratio and may argue on a case-by-case basis [11, 12].

Although both racemic and single enantiomer drugs will continue to be developed, a higher proportion of single enantiomers are being submitted for new drug approval. For example the (-)-enantiomer of Sotolol has both alpha-blocker and antiarrhythmic activity, whereas the (+)-enantiomer has antiarrhythmic activity but lacks alpha adrenergic antagonism [13, 14]. In addition, the (R)-enantiomer of fluoxetine,

at its highest administered dose, leads to statistically significant prolongation of cardiac repolarization in phase II studies and study was stopped due to adverse reaction [15].

Although many psychotropic drugs are either achiral (eg. Fluvoxamine, nefazodone) or are already marketed as single enantiomers (e.g. sertraline, paroxetine, escitalopram), a number of antidepressants are currently marketed as racemates, including bupropion, ibuprofen, citalopram, fluoxetine, tranylcypromine, trimipramine and venflaxine. Other drugs often used in psychiatric practice including zopiclone, methylphenidate and some phenothiazenes are also available as racemates. Of these, single enantiomer formulations are being developed for buprpion and zopiclone. Dexmethylpenidate (d-methylphenidate) has also been introduced recently. In both cases, one enantiomer appeared to have superior *in-vivo* properties and clinical trials were conducted to determine the safety and efficacy of (S)-citalopram and (R)-fluoxetine. In case of citalopram, the S-enantiomer is primarily responsible for antagonism of serotonin reuptake while the (R)- enantiomer is 30 fold less potent. [16]

In clinical trials, both racemic (R,S)-citalopram (marketed as Celexa) and (S)-citalopram (marketed as Lexapro) were significantly better than placebo for improving depression [17-20]. The early data suggest that (S)-citalopram has greater efficacy than (R,S)-citalopram at doses predicted to be equivalent as well as equal efficacy to (R,S)-citalopram at a dose that produces fewer side effects. Overall, (S)- citalopram appears to have advantages over racemic citalopram and is a good example of potential benefits of single enantiomer drug. However, there is currently no evidence that patients with major depression who are responding well to therapy with R, S-citalopram benefit from switching to S- citalopram [21].

In contrast, the attempt to develop a single enantiomer formulation of fluoxetine for the treatment of depression was unsuccessful. While (R)- fluoxetine and (S)- fluoxetine are similarly effective at blocking serotonin uptake, they are metabolized differently [22]. The use of the R-enantiomer was expected to result in less variable plasma levels of fluoxetine and its metabolites than observed with racemic fluoxetine. Additionally, (R)-fluoxetine and its metabolites inhibit CYP2D6, a cytochrome P450 system enzyme, to a lesser extent than (S)-fluoxetine and its metabolite [23].

Phase-II studies of (R)-fluoxetine shown that it led to prolong the cardiac repolariozation, and the studies were stopped. Although since last 15 years, racemic fluoxetine has been shown to be a safe and effective antidepressant, but due to safety concern, the (R)-enantiomer formulation was not viable [23]. The clinical findings highlighted that (S)-citalopram and (R)-fluoxetine have potential differences between enantiomers of a given chiral drug and the need to consider single enantiomer formulations of a previously racemic drug on a case- by-case basis is mandatory. Various single enantiomer products are available in market as mentioned in table 2 showing the top selling brands.

Therefore it is observed that optically pure enantiomers have great advantage in chiral drug development and it leads to develop a molecule of low dose, low metabolic load and higher efficacy to elicit the desired response.

Chirality and biological activities of different enantiomers

The correlation between structure and activity has been a major tool in contemporary biochemical, biomedical research, rational drug design and disease discovery. Chiral phenomena are common in living systems. Life and chirality are strictly connected. At a molecular level, chirality represents an intrinsic property of the 'building blocks of life', such as amino

Table 2. Top selling single enantiomer drugs, global 2005 sales

Company name	Brand name	Active pharmaceutical ingredient	2005 sales(in $ billions)
Pfizer, Astellas Sanofi-Aventis	Lipitor	Atorvastatin	12.986
Bristol-Myers Squibb	Plavix	Clopidogrel	6.345
Amgen, Johnson & Johnson	Apogen, Procrit	Apoetin alpha	5.799
GlaxoSmithKline	Advair, Seretide	Flutecasone and salmeterol	5.465
Genentech, Rosch	Rituxan, Mapthera	Rituximap	5.166
AstraZeneca	Nexium	Esometrazole	4.633
Merck & Co.	Zocor	Simvastatin	4.382
Diichi Sankyo	Mevalothin	Pravastatin	3.844
Bristol-Myers Squibb	Pravachol	Pravastatin	3.844
Novartis	Diovan	Valsatran	3.676
Amgen, Wyeth	Enbrel	Etanercept	3.567
Johnson & Johnson,Schering-Plough	Remicade	Infliximap	3.477
Amgen	Aranesp	Darbepoitin alpha	3.276
Pfizer	Zoloft	Sertraline	3.256
Merck & Co	Singulair	Montelukast	2.976
Sanofi-Aventis	Lovenox	Enoxaparin	2.668
Genentech, Rosch	Herceptin	Trastuzumab	2.469
Amgen	Neulasta	Pegfilgrastim	2.288
Lundbeck, Forest laboratories	Cipralax, Lexapro	Escitalopram	2.043
Pfizer	Zithromax	Azithromycin	2.025
Sanofi-Aventis	Taxotere	Docetaxel	2.003
Sanofi-Aventis	Eloxatin	Oxaliplatin	1.947

acids, sugars, peptides, proteins and polysaccharides. As a result, metabolic and regulatory processes occurring in biological systems are sensitive to stereochemistry and different responses may be observed when comparing the activities of enantiomers [24].

Complexes formed between a receptor and two enantiomers are diastereomers, not enantiomers and as a result they have different energies and chemical properties. The chiral antihistamine dexchlorpheneramine is highly stereoselective; the S-(+)-isomer is about 200 times more potent than R-(+)-isomer [25].

Therefore the activity of the enantiomer is the result of interaction between itself and active sites of biological system. Hence, it is important to understand the interaction of optically active drug at its stereochemical level with enzymes/ receptors as well as how they are capable of producing different therapeutic effect at mechanistic level.

In the example depicted in fig. 1 hydroxyl group of R-(-)-epinephrine can better fit with the active site in enzymes and produce desired therapeutic effect efficiently but hydroxyl group of S-(+)-epinephrine can not accommodate itself in the active site or may have an adverse steric interaction.

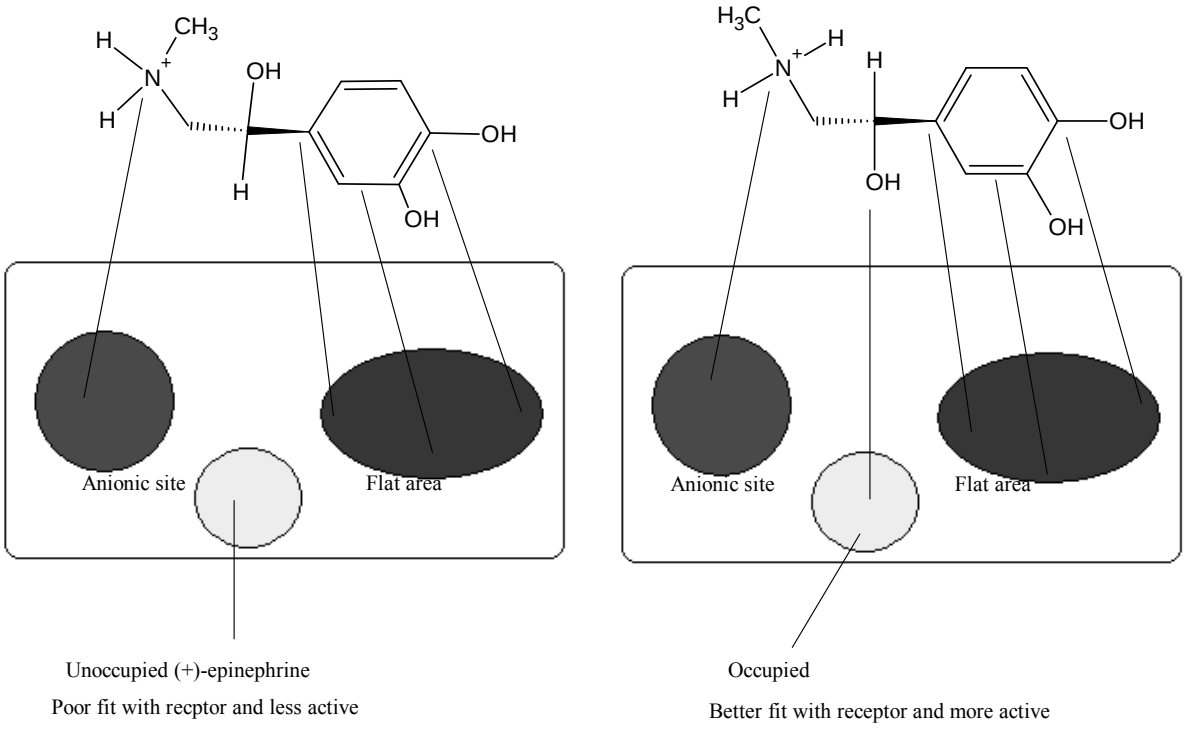
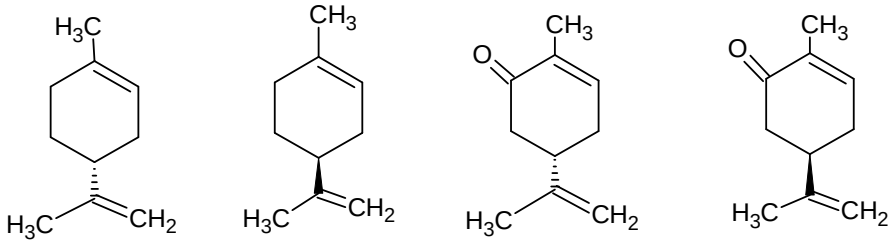


Figure1: Interaction of epinephrine enantiomers with receptor

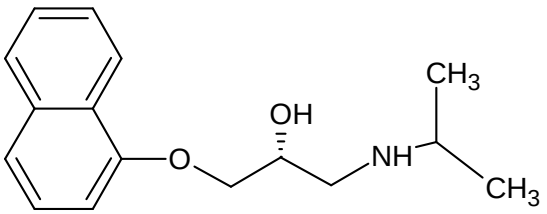


(R)-(+)-	(S)-(-)-	(S)-(+)-	(R)-(-)-
Limonene		Carvone	
Odor:			
orange	Lemon	Caraway	Peppermint

Consequently it has lower binding energy and has less active than R-(-)-epinephrine.

Chirality is a fundamental property of biological systems and reflects the underlying asymmetry of matter. Interactions of drugs with receptors, enzymes or binding sites have long been known to be stereoselective, and it is increasingly recognized that both pharmacodynamic and pharmacokinetic events contribute to the overall clinically observed stereoselectivity [26].

Due to the chiral nature of amino acids (except glycine), drug binding sites of proteins are asymmetric. In the past, the different actions of enantiomers of chiral molecules on enzymes and receptors were often neglected. For economic reasons, racemates of synthetic drugs were used in therapy. Today, researchers and drug companies are more aware of the different effects of enantiomers and diastereomers, in their biological activities as well in their pharmacokinetics like in following example [27-30].



(-)-Propranolol

Eudismic Ratio:

for beta1 receptor 100

for anaesthic activity 1

Sensory receptors are G-protein coupled receptors that differentiate between enantiomers, like all other receptors. Correspondingly, enantiomers can even be recognized by their characteristic odor, *e.g*. the monoterpenes (*R*)- and (*S*)-limonene and (*R*)- and (*S*)-carvone [31] or by their odor intensity, e.g. some diastereomeric wine lactones[32].

Eudismic ratio in chiral drug development

The origin of chiral drugs lies in the rational drug design process as which is targeting the enzymes and receptors. The 'Pfeiffer rule' stated that lower the effect dose of a drug, the greater the different in the pharmacological effect of optical isomers [33].

The initial finding that the logarithm of the ratio of the potencies or efficacies of enantiomers for a number of drugs was proportional to the logarithm of the administered dose was the starting point for eudismic analysis in pharmacology and related disciplines [34]. The ratio between the potencies or efficacies is called the eudismic ratio or stereospecific ratio, and its logarithm is referred to as eudismic index or stereospecific index. Pfeiffer"s rule states that the eudismic index should increase linearly with increasing efficacy or potency of the eutomer [35].

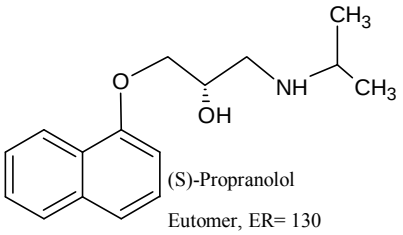
It has been proposed that the active enantiomer of a chiral molecule be termed eutomer whilst the less active enantiomer should be termed the distomer. The eudismic ratio (ER) is defined as the ratio of the activity of the eutomer to that of distomer. The presence of the distomer in the chiral drug can have a number of consequences on biological system [36].

Higher the ratio, higher the potency of eutomer:

The enantiomeric activity is described on the basis of eudismic ratio which is the ratio of more potent enantiomer (eutomer) to less potent enantiomer (distomer). The *in-vivo* eudismic ratio (-/+) for analgesic agent etorpine is greater than 6666. Propranolol, the first member of beta blockers (is competitive of beta-adrenergic recptors) which reduce the blood pressure and regulates cardiac rhythm and oxygen consumption for those with cardiac disease. The eudismic ratio (-/+) for propronol is about 100; however, propronolol also exhibits local anaesthetic activity for which the eudismic ratio is 1 [37- 38].

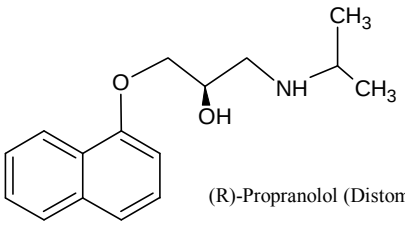
The eutomer is more potent than distomer or distomer is inactive:

The increase in eudismic ratio, with an increase in potency of eutomer according to Pfeiffer rule but small eudismic ratios are observed when the eutomer has low affinity for the receptor (poor molecular complementarily). The eudismic ratio determines the therapeutic effect of the enantiomers. In the case of antihypertensive agents (beta-blocker) propranolol, the (S)- enantiomer is 130 fold more potent than (R)- enantiomer as beta adrenoceptor antagonist which has shown the eudismic ratio 130. A number of other beta blockers are based on this structure show high eudismic ratio. Some drugs shows greater enantioselectivity like dexetimide has 10000 fold greater affinity

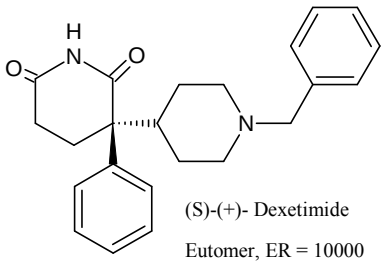


(S)-Propranolol

Eutomer, ER= 130

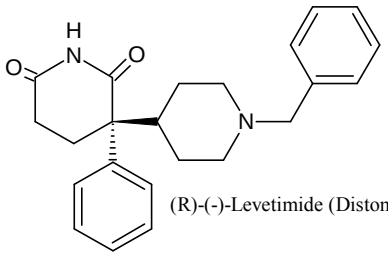


(R)-Propranolol (Distomer)



(S)-(+)- Dexetimide

Eutomer, ER = 10000



(R)-(-)-Levetimide (Distomer)

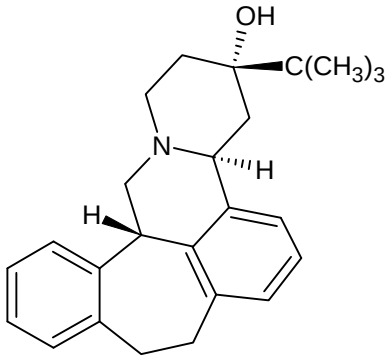
Receptor	Eudismic ratio for (+)-Butaclamol
α_1 receptor	73
D_1 receptor	160
D_2 receptor	1250
r-HT_1 receptor	8
5-HT_2 receptor	73
Muscaranic Ach receptor	0.8

for the muscarinic acetylcholine receptor than levetimide.

The distomer in such case is considered as isomeric ballast. In the case of high eudismic ratio, the distomer is inactive [33].

It is quite common that the chiral compounds shows the seteroselectivity with the receptor action like (+)-Butaclomol is potent antipsychotic, but the (-)- isomer is essentially inactive; the eudismic ratio (+/-) is 1250 for D_2-dopaminergic, 160 for D_1-dompaminergic and 73 for alpha-adrenergic receptors [39]. (-)-Baclofen is a muscle relaxant that binds to the GABA receptor; the eudismic ratio (+/-) is 800. [40] and (+)-cyclazosin displays selectivities of 1100-, 19000- and 12000-fold in binding to α_{1B} adrenoceptor *vs.* α_2- adrenoceptor, 5-HT_{1A} and D_2-receptors, respectively [41, 42]. The eudismic ratio for Butaclamol is depicted in table 3.

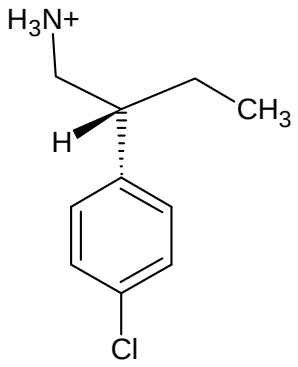
Table 3:



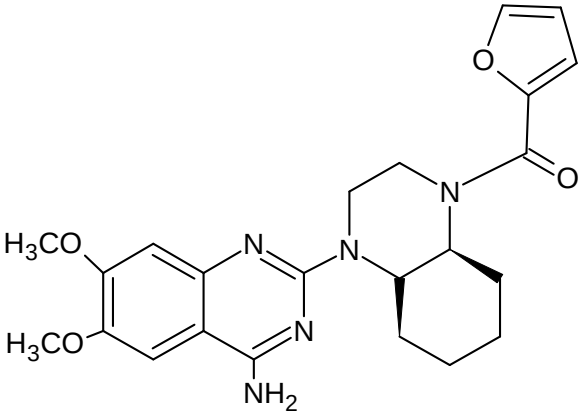
(+)-Butaclamol

Calcium channel blockers have their ability to inhibit entry of calcium ion *via* a subset of channels, thereby leading to improvement of contraction. It was found that in case of these compounds the eutomers are usually S-enantiomers. Their eudismic ratios are in range from 2 for nimodipine to 1000 for amlodipine [43, 44]. Amlodipine is a mixture of two enantiomers, one (S) having L-type channel blocking activity, whereas the (R)-enantiomer releases NO [45].

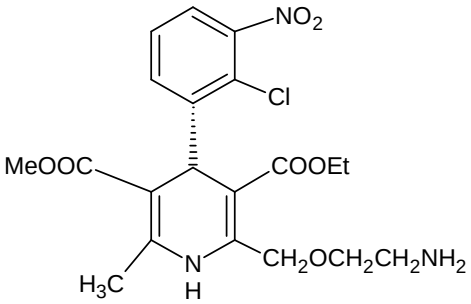
Additionally, pharmacokinetics studies showed no significant differences between behavior of R-(+) and S-(-)-enatiomers. On the other hand, different pharmacokinetic behavior was observed for nicardipine . Serum concentration of (+)-nicardipine, playing a major role in blocking calcium channel, were found to be twice higher than those of (-) one [46-48].



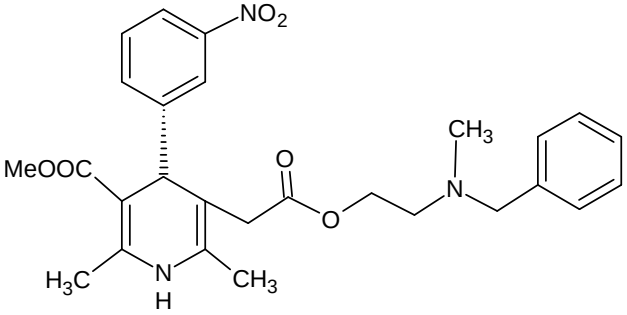
(-)-Baclofen



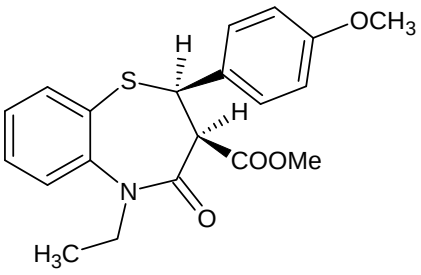
(+)-Cyclazosin



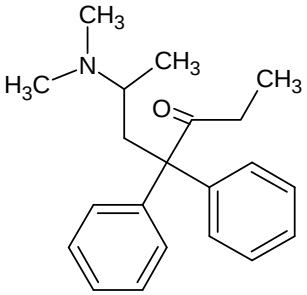
Amlodipine



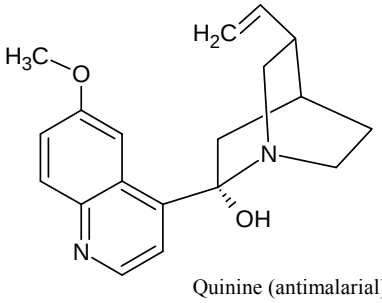
Nicardipine



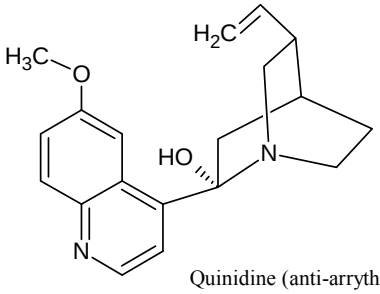
Diltiazem



Methadone



Quinine (antimalarial)



Quinidine (anti-arrythmic)

Diltiazem, a benzothiazepine derivative that contains two chiral centers, is a voltage-dependent calcium channel antagonist used in treatment of arrhythmia. It was found that (+)-diltiazem with configuration (2*S*, 3*S*) is a voltage-dependent calcium channel and possesses ability to protect the myocardium against the injury caused by ischemia or reperfusion. Its optical isomer (-)-diltiazem displays 20–100 times lower calcium blocking activity than (+) form, but like (+) isomer possesses cardioprotective action [49].

Methadone is a racemate, the R-enantiomer being the pharmacologically active form of the drug. This isomer shows a 10-fold higher affinity for the mu and delta opioid receptors, and nearly 50 times the antinociceptive activity of the S-enantiomer [50].Other drugs are Dexketoprofen, Dexibuprofen, Esomeprazole, Levobupivacaine, Escitalopram, Levocetirizine etc. One isomer of these drugs is active while other is inactive.

Both the enantiomers have independent therapeutic effects:

In some cases, both the enantiomers are having their therapeutic effects and both the enantiomers are acting as eutomers depending upon the desired activity. The classical example of this behavior is quinine and quinidine. The first stereoselective synthesis of quinine has recently been published by Stork and coworkers. Quinidine, on the other hand, is used as class 1A anti-arrhythmic agent and acts by increasing action potential duration [51].

The drug dextropropxyphene marketed by Eli Lilly has trade names reflecting the different activities of the enantiomers. Thus the (2R,3S)-enantiomer, DARVON has analgesic activity whilst the (2S,3R)-enantiomer NOVRAD is an antitussive (preventing or relieving coughing)

Distomer possesses harmful effects:

In some cases, it is known that the distomer produces harmful or undesirable side effects. Thus, dexomethorphan is used as a cough suppressant, whereas levo-methorphan has antitussive properties it is also an opioid narcotic.

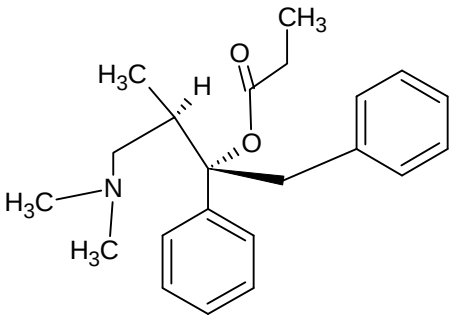
The eutomer and distomer have the opposite biological activity:

It is sometimes observed that the enantiomers of chiral drug may have opposite biological activity. The example of this class is (-)-dobutamine which is an agonist at alpha-adrenoceptors whereas (+)-dobutamine is an antagonist. However, (+)-dobutamine is ten fold more potent than the (-)-dobutamine as $beta_1$ adrenoceptor agonist and is used to treat cardiogenic chock. The individual enantiomer of the 1,4-dihydropyridine analog BayK8644 have opposite effects on L-type calcium channels with the (S)-enantiomer being an activator which stabilize the open calcium channel and the (R)-enantiomer as antagonist stabilize the closed channel [52-54].

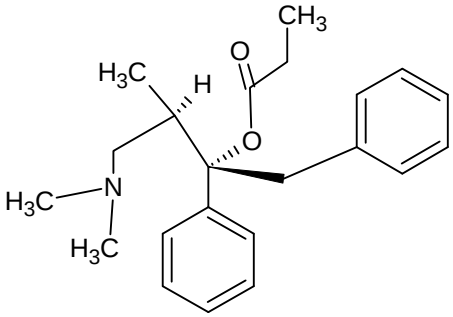
Sometimes it was also observed that enantiomers have opposite effects. The (R)-(-)- enantiomer of 1-methyl-5-phenyl-5-propyl barbituric acid is narcotic and (S)-(-)-enantiomer of 1-methyl-5-phenyl-5-propyl barbituric acid is anticonvulsant. The racemate of UH-301 exhibit no serotonergic activity because (R)-UH-301 is an agonist of the $5HT_{1A}$ receptor but (S)-UH-301 is an antagonist of the same receptor. Consequently, no activity is observed with the racemate [36].

The racemate is superior over the individual enantiomer:

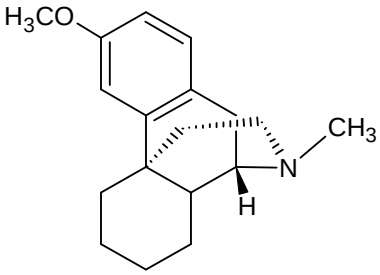
Chiral drugs exhibiting such behavior are quite rare.Recently reported that racemic 3,4-dicarboxyphenylglycine (DCPG) displays a greater potency in preventing sound induced seizures in an experiment of generalized epilepsy seizures rather than either enantiomer alone. The (R)-enantiomer of DCPG has antagonist activity at the AMPA receptor subtype of ionotropic glutamate receptors whereas (S)-enantiomer has agonist activity at the mGlu8 receptor subtype of metabotropic glutamate receptors [55].



DARVON (analgesic)

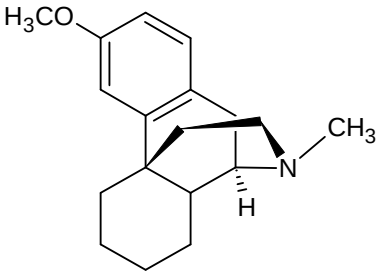


NOVRAD (antitussive)



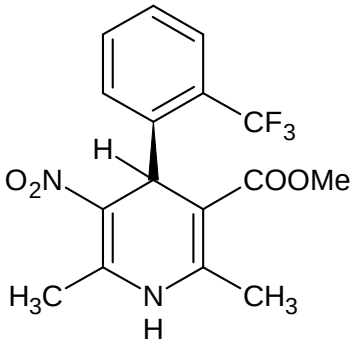
Dextromethorphan

(Cough supressant)



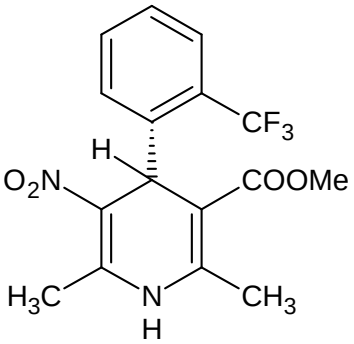
Levomethorphan

(Narcotic)



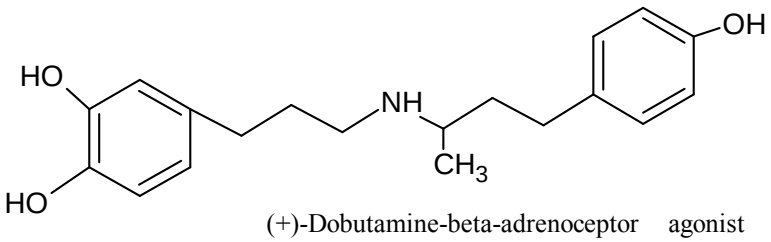
(S)-BayK8644

activator of L-type Ca^{2+} channel



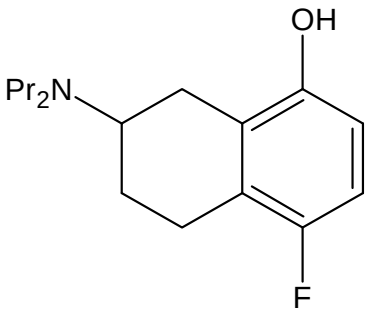
(R)-BayK8644

antagonist of L-type Ca^{2+} channel

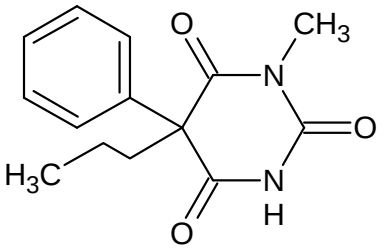


(+)-Dobutamine-beta-adrenoceptor agonist and alpha adrenocpetor antagonist

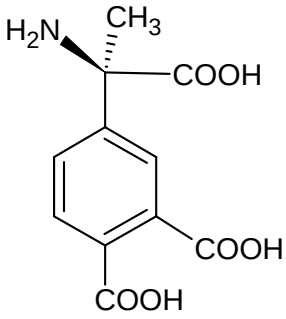
(-)-Dobutamine-betadrenoceptor agonist and alpha adrenoceptor agonist



UH-301



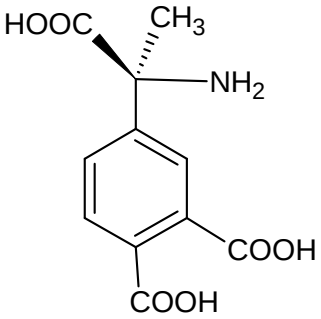
1-methyl-5-phenyl-5-propyl barbituric acid



(R)-DCGP

AMPA recepto antagonist

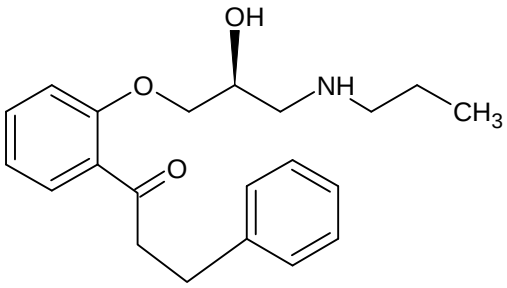
No action on mGlu8



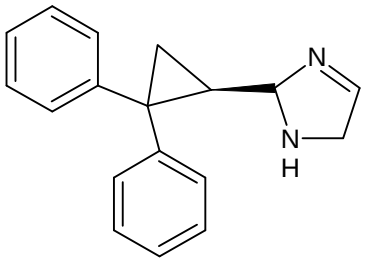
(S)-DCGP

No effect on AMPA receptor

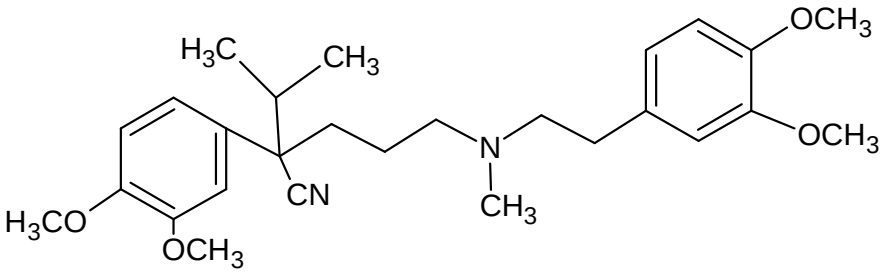
mGlu8 recepto agonist



Propafenone



Cibenzoline

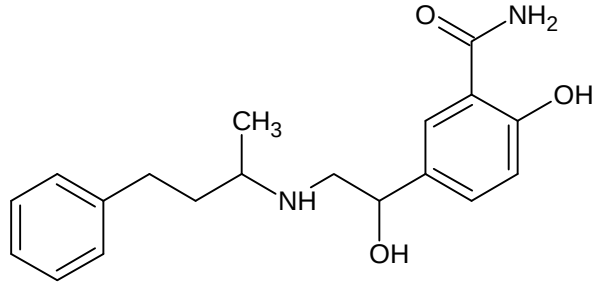


Verapamil

Propafenone (PPF) is a chiral antiarrhythmic drug used clinically as a racemic mixture. Although both enantiomers are equally potent in their activity as sodium channel blockers, the S-(+)-enantiomer exhibits 100-fold higher β-blocking activity. It has been demonstrated that R-enantiomer is cleared faster than S one, leading to higher concentration of S-form in plasma after administration of racemic PPF to humans. Additionally, in vitro studies on human microsomal preparations have shown that enantiomer/enantiomer interaction between S- and R-PPF was inhibited by (R)-PPF [56-59].

These metabolic differences occurred only at higher concentrations of drug, and their mechanism, might involve enantiomeric difference in enzymatic catalyzing ability and/or affinity to the substrate [60- 61].

Labetalol was originally introduced as a drug that blocks both a- and b-adrenoceptors with the understanding that both properties reside in the same molecule. This was a remarkable new finding since antagonists selective for a-adrenoceptors known at that time did not block b-adrenoceptors and vice versa. However, labetalol has two chiral centres and consists of an equal mixture of four stereoisomers [62].



Labetolol

When all four isomers were examined, it appeared that the non-selective inhibitory effect at b-adrenoceptors resides in the (R;R)-isomer while the (S;R)-isomer is largely responsible for antagonism at a1-adrenoceptors [63].

The two remaining isomers were weaker as inhibitors. It was concluded that the adrenoceptor blocking profile of labetalol is not attributable to the properties of any individual stereoisomer; instead each of the stereoisomers contributes to the overall effect of labetalol. The pure (R;R)-enantiomer of labetalol, given the generic name dilevalol, was later found to possess partial agonist activity at b2-adrenoceptors [64]. While dilevalol had the advantage of not producing postural hypotension, it never reached the market owing to hepatoxicity not seen to the same extent with labetalol. So it came that labetalol continued to be marketed as a racaemic mixture of four stereoisomers.

As a matter of fact, it comprises a fixed ratio mixture of four drugs with one fourth each. It is unknown whether this given ratio is optimal for a well balanced hypotensive effect [65]. Verapamil, L-type calcium antagonist, is a phenylalkylamine derivative. This drug is marketed as a racemate and is employed in treatment of hypertension, arrhythmia and angina pectoris. The enantiomers of verapamil have various pharmacokinetic properties and, hence, differ in bioavailability and pharmacological activity.

The S-(-) enantiomer is about 20 times more potent than the R-(+) in both cardiac and cardiovascular preparations. (S)-verapamil has both vasodilating and cardiac depressant properties, while (R)-isomer is predominantly a vasodilating drug. (S)-verapamil is also characterized by approximately double first pass effect as compared to the (R)-antipode [66-68].

Cibenzoline is a sodium channel blocker that also exhibits potassium and calcium channel blocking activity. It is used as a racemic mixture but S-(-)-enantiomer is approximately twice more potent that the R-(+). Additionally, its R-isomer is preferably (about 23 times more) metabolized [69]. Other drugs which are administered as racemate are tricyclics, mianserin, mirtazepine, fluoxetine, reboxetine, venlafaxine, citalopram [70].

Table 4: Eudismic ratio and stereoselectivities of some chiral beta agonists

Drug	Experimental model	Pharmaceodynamic response	Direction of steeoselectivity (Eudismic ratio)	Reference
Clenbuterol	Mouse	Antidepressant activity	R>S	80
	Guinea pig trachea	Relaxation of trachea	R>S, 1000	81
	Guinea pig trachea	Blocking isoprenaline	R>S, 100	81
Albuterol	Dog	Reduction of pulmonary resistance	R>S, 50	74
	Guinea pig	Inhibition of bronchospasm	R>S, 40	74
	Guinea pig tachea	Induced tone reduction	R>S, 80	75
Trimethoquilon	Guinea pig trachea	Bronchodilation	S>R,S, 2	78
	Guinea pig	Bronchodilation	S>R,S, 15	79
	Human Platelets	Antiaggregation	R>S, 7	79
Formeterol	Guinea pig trachea and rabbit	Mucocilliary activity	R>S, 22	79
Terbutaline	Guinea pig trachea	Trachea ralxation	R>S, 33	

Eudismic ratio and stereoselectivity in the pharmacodynamics of β_2-agonists has been extensively studied at both the receptor and the end-clinical response levels sown in table 4. Except for trimethoquinol, the bronchodilator action of all β_2- agonists is predominantly due to the R-enantiomer. The study on tissues from various animals and humans, it has been observed that β_2-adrenoceptor agonist activity resides mainly with the R or (R,R) isomers of racemic albuterol, terbutaline, formoterol, and clenbuterol and showing that its eutomer has significant therapeutic efficacy than the distomer [71–84].

Conclusion:

The rationale for the development of the chiral compounds as single optically pure enantiomer has advantageous as it shows the superior therapy by allowing the reductions in the dosage, reduced variability in metabolism and response, simpler dose response relationships and improved tolerability. Each enantiomer interacts with the enzymes/proteins /receptors differently and responds differently by eliciting different therapeutic effect. Hence the currently available facts suggest that for enantiomers of many chiral drugs, there are clear functional differences between the distomer and eutomer. It represents that eudismic ratio of the chiral drugs plays an essential role in drug designing that higher the eudismic ratio, better the therapeutic action of the chiral molecule. Therefore, the pharmaceutical industries are looking for the development of optically pure enantiomers to reduce the risk of distomer in our body and the higher eudismic ratio considered as an important tool in drug discovery and drug designing.

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