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MOLECULAR BIOPHYSICS

On the Chirality of Drugs and the Structures of Biomacromolecules

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Abstract—The development of the concept of the role of chirality in the structural formation of biomacromolecules has been demonstrated using correlations between the chiral form of a drug and its bioactivity. Understanding the nature of the chiral-hierarchical structure of target biomacromolecules and the symmetry structure of drugs is of great importance for establishing the possible systematic character of chiral correspondences between drugs and targets. It is crucial to take the stereoselectivity of drug-target interactions into account when creating drugs because one chiral form of the drug may have a therapeutic effect but the other one may be non-digestible, weakly active, cause severe side effects, or be toxic. The bioactivity of chiral drugs has been discussed, and hypotheses put forward about a possible relationship between drug chirality and the drug effect on a specific chiral molecular target.

Keywords: chirality, enantiomers, chiral drugs, stereoselectivity, structure hierarchy

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An important structural feature of many biological molecules and medicinal compounds is chirality, i.e., the noncoincidence of an object with its mirror image in any combination of movements and rotations in three-dimensional space. Two chiral molecules, which mirror each other are called enantiomers, and two molecular structures of a higher level are called enantiomorphs. Enantiomers have the same physicochemical properties (boiling and melting points, density, etc.) but differ in their optical activity, i.e., the magnitude and sign of rotation of the polarization plane. Enantiomers including those among drugs can exhibit completely different chemical specificity and biological activity in processes involving chiral compounds. When creating and using medicines, it is extremely important to take the chirality of the drug into account because one enantiomer of the drug may have a therapeutic effect but its counterpart may be less active or completely inactive, or even cause serious side effects in some cases. This phenomenon has attracted the attention of the scientific community for many years [1–4]. A well-known example of a drug which illustrates the importance of chirality in the drug design is thalidomide [5–8]. From 1957, this drug was used as a tranquilizer and a sleeping pill and was prescribed to pregnant women to combat morning ailments. However, as early as 1959, reports of cases of peripheral neuropathy began to appear in patients who had been taking thalidomide for a long time. Soon after that, it was found that the probability of having children with congenital limb defects increases dramatically in pregnant women taking this drug. Thalidomide was marketed as a racemic mixture, and later it was found that only the R-isomer of thalidomide has a therapeutic effect, while the S-isomer has a teratogenic effect [5, 8].

More than half of currently used medicines are chiral drugs, and most of these chiral drugs are racemates [3]. More than half of the drugs developed in recent years also consist of chiral molecules. Chiral drugs are used in the treatment of a wide range of diseases including cardiovascular and gastrointestinal disorders. The synthesis of optically pure forms of these compounds is a complex and expensive task. However, their use may reduce the dosage and side effects of the drug in many cases.

The bioactivity, pharmacodynamics, and pharmacokinetics of enantiomers and the process of chiral inversion of optical isomers in living systems are currently being intensively studied [9–12]. It is possible that the systemic tendency of alternating the sign of chirality at the structural and functional levels of proteins and DNA, which we earlier identified, will help to make a step towards a better understanding of the interaction of a chiral drug with a chiral target [13–15].

NOMENCLATURE

There are several variants of the nomenclature for the designation of enantiomers (Fig. 1). Enantiomers are distinguished by their optical activity ((+)/(–)-

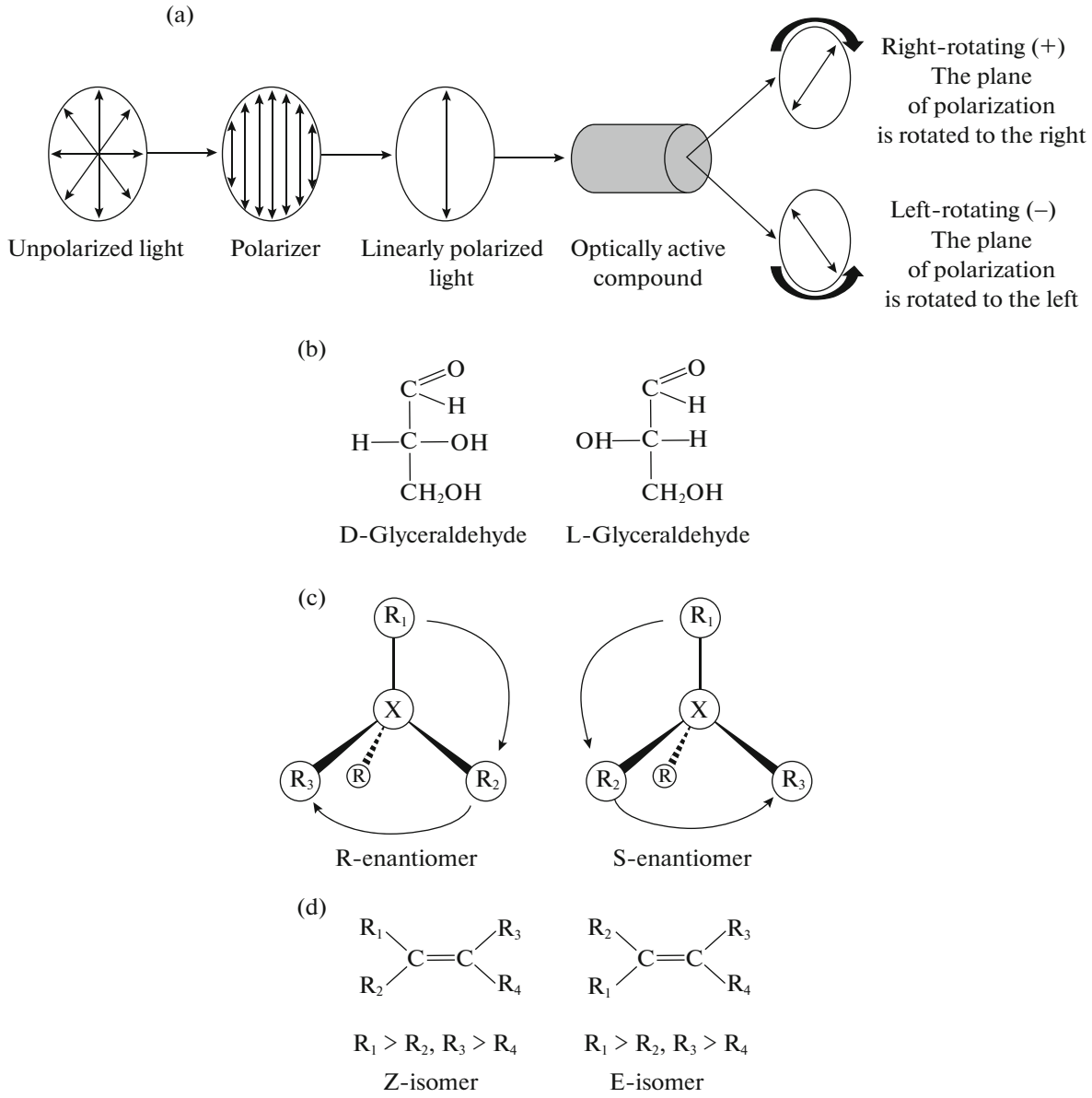

Fig. 1. Designations of stereoisomers following optical activity(a), L/D nomenclature (b), R/S nomenclature (c), and E/Z nomenclature (d).

nomenclature) and their accepted absolute configuration (L/D- and R/S-nomenclature). Due to the large number of variants of names, there may be some confusion.

In 1848, L. Pasteur made the first discovery related to the optical activity of molecules. He obtained asymmetric crystals of sodium-ammonium tetrahydrate from a solution of the acidic sodium salt of tartaric acid [16, 17]. It turned out that solutions of two types of crystals had opposing optical rotation. After precipitation of lead or barium salt from the solution and displacement of the weak organic acid with strong sulfuric acid, two enantiomers of tartaric acid were formed, i.e., right-rotating (rotating the plane of polarization of linearly polarized light to the right side, clockwise) from one solution and left-rotating (rotating the plane of polarization of linearly polarized light to the left, counterclockwise) from the other. The right-rotating and left-rotating enantiomers were called D-tartaric acid (from Latin word *dexter*, right, also denoted by "+") and L-tartaric acid (from Latin word *laevus*, left, denoted by "–"), respectively. It turned out that inactive grape acid is a mixture of the well-known right and previously unknown left tartaric acids in an equal ratio. This mixture was called racemate (from Latin word *racemus*, grape). In addition, an optically inactive achiral mesotartaric acid was soon obtained.

Previously, it was impossible to determine the true spatial configuration of the molecules of an optically active substance but it was possible to identify the similarity of the configurations of different substances. In 1891, E.G. Fischer proposed an image of the structures of organic molecules, the Fischer projection, including that for glyceraldehyde [18]. In 1906, M.A. Rozanov proposed glyceraldehyde as the standard for establishing the relative configuration of optically active molecules [19]. Compounds which are stereochemically similar to the right-rotating glyceraldehyde belong to the D-series, and those related to its optical antipode belong to the L-series. The relative configuration of enantiomers in the Fischer system was determined by the transition of this molecule to D- or L-glyceraldehyde through a sequence of chemical reactions, which did not affect the asymmetric carbon atom [18]. It should be noted that correlation between the configurations of glyceraldehyde and a molecule significantly different in structure can be quite difficult using chemical methods.

In 1966, a system of universal description of stereoisomers, the Cahn–Ingold–Prelog nomenclature R/S, was published [20]. To establish the absolute configuration of a compound, the substituents at the asymmetric center are numbered according to the sequential precedence order. The substituents are observed from the furthest side from the most junior substituent. If the direction of decreasing seniority coincides with the clockwise or counterclockwise movement, the configuration of the asymmetric center is indicated by the symbol R (from Latin word *rectus*, right) or S (from Latin word *sinister*, left), respectively. The rules of sequential precedence were specially intended to be in maximum compliance with the early Fischer systematics. As a result, most D-stereoisomers and, very importantly, glyceraldehyde have the R-configuration, and L-stereoisomers often belong to the S-series. In addition, the Cahn–Ingold–Prelog rules (E/Z nomenclature) is used to describe configurations of molecules with double bonds.

It is important to note that the right or left rotation of the enantiomer has no unambiguous correlation with the actual mutual arrangement of atoms in space and, therefore, has no direct relation to the D/L or R/S rules. Compounds with the same sign of rotation can have opposite absolute configurations. Therefore, the optical activity of the compound can be indicated next to the D/L- or R/S-names.

CHIRAL DRUGS AND PHARMACOLOGY

It is known that opposite enantiomers of drugs can exhibit different biological activity when interacting with chiral compounds despite the same physicochemical properties. This feature must be taken into account when using and developing drugs because only one enantiomer of the drug may be therapeutically effective, while the other may be less active, completely inactive, or cause serious side effects.

In this work, we have formed a set of 100 chiral drugs based on the literature. The selected drugs were classified according to the bioactivity of R/S-enantiomers and (+)/(–)-isomers. The targets for exposure of the considered drugs were also identified. Based on the resulting classifications, the drugs were divided into three groups, i.e., drugs with a bioactive left S-enantiomer, drugs with a bioactive right R-enantiomer, and drugs with two bioactive enantiomers (Fig. 2). In the first group, two subgroups have been additionally identified, which contain as counterparts either the R-enantiomers responsible for side effects or less active or inactive R-enantiomers. Similar subgroups were identified among the "right" drugs.

Drugs that contain a bioactive left S-enantiomer. Most of the drugs in the set contain the bioactive left S-enantiomer. This group of drugs was divided into two subgroups, which contain as counterparts either the R-enantiomer responsible for side effects or the R-enantiomer with a lower therapeutic effect or no therapeutic effect.

*Drugs that contain a bioactive left S-enantiomer along with a right R-enantiomer responsible for side effects***.** A representative of this group, an antitussive agent dropropizine, has been used for a long time in therapy as a racemate. However, it was found that the S-enantiomer of dropropizine exhibits the same antitussive activity as the racemic mixture while having a lower effect on the central nervous system [21]. Currently, there are few safe and effective drugs for the treatment of cough. The poor tolerability of most available antitussives is closely related to their action on the central nervous system. Therefore, S-dropropizine, due to its lower effect on the central nervous system, is a safer and well-tolerated drug for treating cough [22].

Prilocaine, a local anesthetic, is often used for conduction anesthesia and local anesthesia. Both enantiomers have the same biological activity. However, the S-enantiomer hydrolyzes slowly, whereas the quick hydrolysis of the R-enantiomer leads to the formation of toluidine, which causes methemoglobinemia [23].

Naproxen, a nonsteroidal anti-inflammatory agent, is used in an enantiomerically pure form, i.e., only as the S-isomer because the R-enantiomer exhibits 28 times less anti-inflammatory activity and is toxic to the liver [24, 25].

The "left" drugs, which contain a right R-enantiomer responsible for side effects, also include drugs such as bupivacaine [26], halothane [27], halofantrine [28], ketoprofen [29], clopidogrel [30], metoprolol [31], penicillamine [32], fenfluramine [33], and ethambutol [34].

Drugs that contain a bioactive left S-enantiomer and right R-enantiomer with a lower therapeutic effect or no

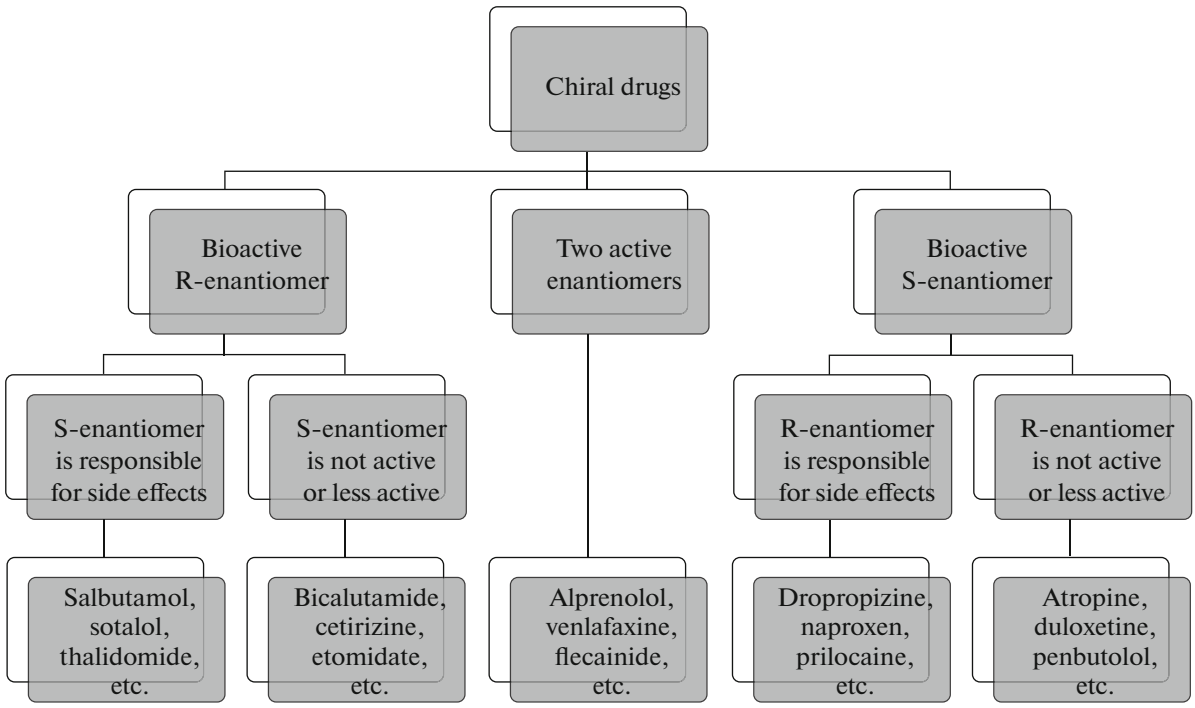

Fig. 2. Three groups of drugs identified according to the sign of chirality of the bioactive enantiomer with the bioactive left S-enantiomer, bioactive right R-enantiomer, and two bioactive enantiomers.

therapeutic effect. The drugs of this subgroup in our set include the following medicinal agents: amlodipine [35, 36], atenolol [37], atropine [38], benazepril [39], benzetimide [40], bisoprolol [41], bunolol [10, 42], valsartan [3], warfarin [43, 44], verapamil [45], vigabatrin [46], dopamine [47], duloxetine [48], zopiclone [49, 50], ibuprofen [51], carvedilol [52], ketamine [53], ketorolac [54], clidanac [55], melphalan [56], mepivacaine [57, 58], methotrexate [59], moprolol [10, 60], oxazepam [3, 61], omeprazole [62], ofloxacin [63], pantoprazole [64], penbutolol [10], pindolol [65], pregabalin [66, 67], propranolol [68, 69], ropivacaine [70], tetramisole [71], thiamylal [72], timolol [73], thiopental [74, 75], fenoprofen [76], phenprocoumon [43], chlorpheniramine [77], celiprolol [10, 78], citalopram [51, 79], enalapril [80], esmolol [81].

Both enantiomers of duloxetine are inhibitors of norepinephrine and serotonin reuptake. However, it was found that the S-enantiomer of duloxetine is twice as active as the R-enantiomer. Therefore, this drug was introduced into therapy as the S-enantiomer [48].

Penbutolol became the first β-blocker used in the clinic as the enantiomerically pure S-isomer. This isomer was found to be 200 times more active in both *in vitro* and in *vivo* experiments compared to the R-enantiomer, and five times more active than the reference drug propranolol [10].

Atropine, which has a cholinolytic effect, is an M-cholinoblocker. The drug is the racemic mixture of R- and S-hyoscyamine, and the latter has a more powerful antimuscarinic effect compared to R-hyoscyamine or the racemate [38]. Atropine has been used in the racemic form as an antidote for sarin poisoning but its effectiveness has often been questioned. It is believed that the effectiveness of the drug can be increased by using either pure S-hyoscyamine or an atropine sample enriched with S-hyoscyamine, since the latter is more efficient, while R-hyoscyamine is relatively ineffective.

Drugs that contain a bioactive right S-enantiomer. This group of drugs is divided into two subgroups, which contain as counterparts either the S-enantiomer responsible for side effects or the S-enantiomer with a lower or no therapeutic effect.

Drugs that contain a bioactive right R-enantiomer and a left S-enantiomer responsible for side effects. The most striking and well-known example of the bioactive drug, which contains an active right enantiomer with the left enantiomer responsible for side effects is thalidomide. This drug was introduced on the market as the racemic mixture. During the sale of thalidomide, about 10000 children worldwide were born with phocomelia or limb malformation, of which only half of the infants survived [5]. A few years after the start of using the drug, it was found that only R-thalidomide has a therapeutic effect, while S-thalidomide has teratogenic properties [5–8]. According to recent studies, the S-enantiomer of thalidomide demonstrates ten times stronger binding to cereblon (CRBN) and inactivation of self-ubiquitination compared to the R-iso-

mer [8], which confirms the fact that it is S-thalidomide that induces the teratogenic effects.

Another member of this group is terbutaline. It has a bronchodilator effect and is used to relieve asthma. The drug is presented as a racemic mixture, the R-isomer of which selectively excites β-adrenergic receptors, while the S-isomer has practically no affinity for β-adrenergic receptors and causes side effects such as respiratory hyperreactivity and cardiac disorders [82]. These side effects are associated with the ability of S-terbutaline to activate muscarinic receptors, thus generating hyperreactivity of the respiratory tract when taking racemic terbutaline.

Salbutamol is a selective short-acting agonist of the β-adrenergic receptor, which is used to treat asthma and chronic obstructive pulmonary disease. As a rule, the drug is given as a racemic mixture, although it is known that the R-isomer of salbutamol has 150 times greater affinity for the β-receptor compared to the S-isomer [83]. In addition, S-salbutamol is toxic because of indirect inhibition of the positive effects of R-salbutamol, and it can produce inflammatory effects.

The drug sotalol exhibits β-blocking activity and is used for the treatment of various cardiovascular diseases. Its β-blocking activity is mainly provided by R-sotalol, which blocks receptors 14–50 times more efficiently than racemic sotalol, while its S-enantiomer is practically inactive [10, 84]. At the same time, both enantiomers of sotalol are equally effective in blocking potassium channels. However, it is known that S- sotalol increases mortality in patients with ventricular dysfunction and subsequent myocardial infarction [85].

Drugs that contain a bioactive right R-enantiomer and a left S-enantiomer with a lower or no therapeutic effect. This subgroup in our set includes the following drugs: atorvastatin [86, 87], acenocoumarol [88, 89], acetylcarnitine [90], baclofen [91, 92], bicalutamide [93], bufuranol [94], genaconazole [95], deprenyl [96, 97], isoprenaline [98], lansoprazole [62, 99], loxiglumide [100], mexiletine [101, 102], methadone [43, 103], methylphenidate [104], miconazole [71, 105], nicardipine [106–108], oxybutynin [109, 110], pronethalol [111], rabeprazole [112], rolipram [113, 114], sertaconazole [105], sibutramine [115], phenibut [116], formoterol [117], cetirizine [118, 119], epinephrine [120], etomidate [75, 121].

Dextrocetirizine, the S-enantiomer of cetirizine, seems to be ten times less effective than levocetirizine, the R-enantiomer of cetirizine [118, 119].

Etomidate is unique among intravenous anesthetics because it is administered as the active optically pure R-isomer. The anesthetic effect is manifested mainly by the R-enantiomer, which is about five times stronger compared to the S-enantiomer of etomidate [75, 121].

Bicalutamide, a nonsteroidal antiandrogen, is used for the treatment of prostate cancer. The R-enantiomer has much higher antiandrogenic activity than the S-enantiomer, which exhibits very low, if any, activity [93].

Drugs with two active enantiomers. The following drugs belong to this group in our set: alprenolol [122], venlafaxine [123], indacrinone [73, 124], methorphan [125], mirtazapine [126], nimodipine [127], oxaprotiline [128], propafenone [129, 130], thyroxine [131], flecainide [132], fluoxetine [133], cyclophosphamide [3, 73], econazole [105], etodolac [134].

An example of a drug in this group is alprenolol, which is used for the treatment of hypertension, angina, and arrhythmia. The S-isomer of alprenolol has approximately 100 times greater affinity to β-adrenoreceptors than the R-isomer. At the same time, both isomers have equal efficiency in stabilizing membranes [122]. Because of this action, both enantiomers of alprenolol can exhibit a direct cardiodepressive effect including antiarrhythmic action unrelated to their blocking activity of β-adrenergic receptors.

Both enantiomers of flecainide have similar electrophysiological effects [132]. The administration of a single enantiomer does not seem to give an advantage over the racemic mixture.

Venlafaxine, which is used to treat mental illnesses including depression, is available for clinical use as the racemic mixture of the S- and R-enantiomers [123]. The enantiomers of this drug exhibit different pharmacological properties, i.e., S-venlafaxine selectively inhibits the reuptake of serotonin, whereas R-venlafaxine inhibits the uptake of both serotonin and norepinephrine.

In addition to the R/S classification, the drugs were classified according to the bioactivity of their (+)- and (–)-isomers (except for the enantiomers of benazepril, valsartan, phenibut, and enalapril).

Analysis of data on the bioactivity of enantiomers of drugs. The data on the clinical efficacy of enantiomers of drugs are summarized in Table 1.

As you can see, most of the drugs (55 out of 100 drugs) from our set are the preparations with bioactive left S-enantiomers, 31 drugs have a therapeutically active right R-enantiomer, and 14 drugs have two bioactive enantiomers.

It was found that 45 out of 100 right R-enantiomers of drugs show a therapeutic effect, and almost as many preparations (43 out of 100 drugs) are inactive or less active. In turn, most of the left S-enantiomers of drugs (69 out of 100) demonstrate a therapeutic effect. The R-enantiomers of drugs more often cause side effects (12 out of 100 right enantiomers compared to 4 out of 100 left isomers).

Similar relationships were revealed when analyzing the classification of bioactivity of (+)/(–)-isomers. It is worth paying attention to the fact that there are (+)-

Table 1. Clinical efficacy of drug enantiomers

	Drug	Bioactive enantiomer	Enantiomer responsible for side effects	Enantiomer with lower or no effect
1	Alprenolol	Both isomers		
2	Amlodipine	S(–)		R(+)
3	Atenolol	S(–)		R(+)
4	Atorvastatin	R,R(+)		S,S(–)
5	Atropine	S(–)		R(+)
6	Acenocoumarol	R(+)		S(–)
7	Acetylcarnitine	R(–)		S(+)
8	Baclofen	R(–)		S(+)
9	Benzperyl	S,S		R,R
10	Benzethimide	S(+)		R(–)
11	Bicalutamide	R(–)		S(+)
12	Bisoprolol	S(–)		R(+)
13	Bunolol	S(–)		R(+)
14	Bupivacaine	S(–)	R(+)	
15	Bufuranol	R(–)		S(+)
16	Valsartan	S		R
17	Warfarin	S(–)		R(+)
18	Venlafaxine	Both isomers		
19	Verapamil	S(–)		R(+)
20	Vigabatrin	S(+)		R(–)
21	Halothane	S(+)	R(–)	
22	Halofantrine	S(–)	R(+)	
23	Genaconazole	R,R(–)		S,S(+)
24	Deprenyl	R(–)		S(+)
25	Dopamine	S(–)		R(+)
26	Dropropizine	S(–)	R(+)	
27	Duloxetine	S(+)		R(–)
28	Zopiclone	S(+)		R(–)
29	Ibuprofen	S(+)		R(–)
30	Isoprenaline	R(–)		S(+)
31	Indakrinon	Both isomers		
32	Carvedilol	S(–)		R(+)
33	Ketamine	S(+)		R(–)
34	Ketoprofen	S(+)	R(–)	
35	Ketorolac	S(–)		R(+)
36	Clidanac	S(+)		R(–)
37	Clopidogrel	S(+)	R(–)	
38	Lansoprazole	R(+)		S(–)
39	Loxiglumide	R(+)		S(–)
40	Mexiletine	R(–)		S(+)
41	Melphalan	S(–)		R(+)
42	Mepivacaine	S(+)		R(–)
43	Methadone	R(–)		S(+)
44	Methylphenidate	R,R(–)		S,S(+)

Table 1. (Contd.)

	Drug	Bioactive enantiomer	Enantiomer responsible for side effects	Enantiomer with lower or no effect
45	Metoprolol	S(–)	R(+)	
46	Methorphan	Both isomers		
47	Methotrexate	S(–)		R(+)
48	Miconazole	R(–)		S(+)
49	Mirtazapine	Both isomers		
50	Moprolol	S(–)		R(+)
51	Naproxen	S(+)	R(–)	
52	Nicardipine	R(+)		S(–)
53	Nimodipine	Both isomers		
54	Oxazepam	S(+)		R(–)
55	Oxaprotiline	Both isomers		
56	Oxybutynin	R(–)		S(+)
57	Omeprazole	S(–)		R(+)
58	Ofloxacin	S(–)		R(+)
59	Pantoprazole	S(–)		R(+)
60	Penbutolol	S(–)		R(+)
61	Penicillamine	S(–)	R(+)	
62	Pindolol	S(–)	R(+)	
63	Pregabalin	S(+)		R(–)
64	Prilocaine	S(+)		R(–)
65	Pronethalol	R(–)	S(+)	
66	Propafenone	Both isomers		
67	Propranolol	S(–)		R(+)
68	Rabeprazole	R(+)		S(–)
69	Rolipram	R(–)		S(+)
70	Ropivacaine	S(–)		R(+)
71	Salbutamol	R(–)	S(+)	
72	Sertaconazole	R(–)		S(+)
73	Sibutramine	R(+)		S(–)
74	Sotalol	R(–)	S(+)	
75	Thalidomide	R(+)	S(–)	
76	Terbutaline	R(–)	S(+)	
77	Tetramisole	S(–)		R(+)
78	Tiamilal	S(–)		R(+)
79	Timolol	S(–)		R(+)
80	Thiopental	S(–)		R(+)
81	Thyroxine	Both isomers		
82	Phenibut	R		S
83	Fenoprofen	S(+)		R(–)
84	Phenprocoumon	S(–)		R(+)
85	Fenfluramine	S(+)	R(–)	
86	Flecainide	Both isomers		
87	Fluoxetine	Both isomers		
88	Formoterol	R,R(–)		S,S(+)

Table 1. (Contd.)

	Drug	Bioactive enantiomer	Enantiomer responsible for side effects	Enantiomer with lower or no effect
89	Chlorpheniramine	S(+)		R(–)
90	Celiprolol	S(–)		R(+)
91	Cetirizine	R(–)		S(+)
92	Cyclophosphamide	Both isomers		
93	Citalopram	S(+)		R(–)
94	Econazole	Both isomers		
95	Enalapril	S		R
96	Epinephrine	R(–)		S(+)
97	Esmolol	S(–)		R(+)
98	Ethambutol	S,S(+)	R,R(–)	
99	Etodolac	Both isomers		
100	Etomidate	R(+)		S(–)

and (–)-isomers in an equal ratio (8 out of 96 isomers) among the isomers that cause side effects. These data could indicate that most of the S-enantiomers of the considered drugs have left-rotating optical activity, and most of the R-enantiomers have right-rotating activity. However, S(+)- and R(–)-enantiomers are more common in our set, i.e., there is no correlation between optical activity and the location of substituents in space, which is consistent with the literature data.

Our set of chiral drugs was also classified according to the drug type. Preparations that contain the bioactive left S-enantiomer are more likely to exhibit hypotensive, antianginal, antiarrhythmic, and analgesic effects, while those that contain the bioactive right R-enantiomer are more often broncholytic and antifungal agents.

The drug databases [135–137] allowed identification of targets for most of the considered drugs. Proteins are the targets for 94 drugs, DNA molecules are the targets for three drugs, and small molecules, such as protoporphyrin IX and copper ions, are the targets for two drugs. Unfortunately, the databases used do not contain information about the targets for indacrinone. This drug is a loop diuretic [124]. The drug is used as a racemic mixture, the R-enantiomer of which exhibits diuretic activity and the S-enantiomer induces uric acid secretion [73].

ALTERNATING CHIRAL HIERARCHIES OF STRUCTURES IN MOLECULAR BIOLOGY

The phenomenon of chirality (homochirality) is a major feature of biological molecules. Proteins are formed from the left (L) amino acid residues, and nucleic acids contain the right (D) sugars (ribose and deoxyribose) [138]. In the future, we will have to elucidate the correspondence between the active forms of chiral drugs and the signs of chirality of their target biomacromolecules.

Earlier, we distinguished for the first time alternating hierarchies of chiral structures as chiral invariants in sequences from the lowest level of an asymmetric carbon atom in an sp3-hybridization state to superhelices and supramolecular structures in macromolecular systems, i.e., from enantiomers to enantiomorphs, which are characterized by helicity and superhelicity [13–15]. Sign-alternating chiral hierarchies are noted during the transition to a higher level of the structural and functional organization of DNA in the A- and B-form (Fig. 3)

It should be noted that the ranking of structures through sign-alternating chirality does not always literally coincide with their traditional description, thus revealing the fine structure of the levels of hierarchical organization. Returning to proteins, we note that the trivial right-left sign-alternating of chirality in their structural hierarchies is not absolute but always has a reasonable explanation.

In addition, another trend is also manifested in the process of chiral systematization in molecular biology. The intermolecular interactions of macromolecules of the same and different classes seem to depend not only on direct complementary correspondence in their contact zone but also on symmetric (chiral) correspondences involved in the interaction of enantiomorphs, i.e., large-scale intramolecular and supramolecular structures. Thus, the right-handed microfilaments are oriented to interact with the left phospholipids of the cell membrane. The left-handed lamins and microtubules are aimed at interacting with right double DNA helices. When interacting between the same type of macromolecules at different structural levels, as we assume, affinity is characterized by

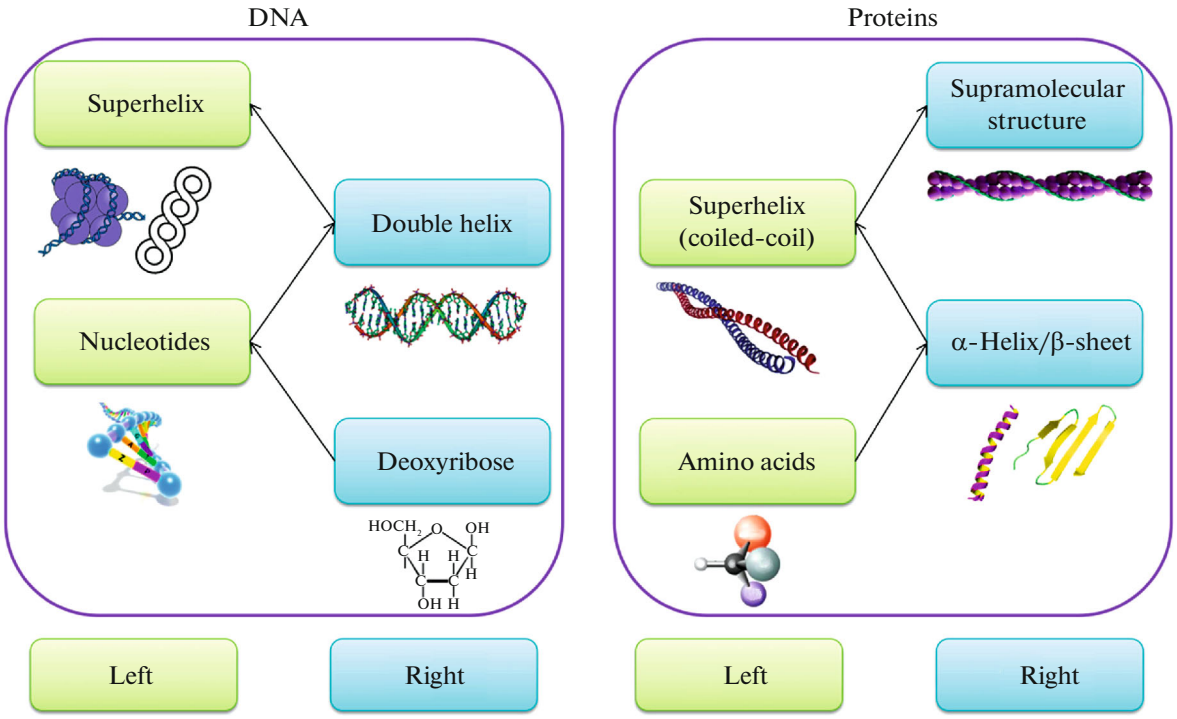

Fig. 3. Sign alternating chirality during the transition to a higher level of structural and functional organization of DNA and proteins.

the same sign of chirality (left–left for protein–protein, right–right for DNA and RNA).

After we have identified and systematized certain patterns in the formation and interactions of the most important chiral biomolecular structures, it seems logical to consider the system of correspondences between chiral drugs and chiral molecular biological structures.

DISCUSSION

Stereospecific interactions of opposing enantiomers with chiral biomacromolecules predetermine the differences in the pharmacodynamic and pharmacokinetic properties of enantiomers. The relationship of these properties of enantiomers with their chiral characteristics can be considered with an example of one of the groups of pharmacological drugs most thoroughly studied in this regard, β-blockers. According to the chemical structure, these drugs can be divided into two groups, i.e., arylaminoethanols and aryloxyaminopropanols [10]. In both groups, the (–)-isomers exhibit greater β-adrenolytic activity, while the arylaminoethanol group includes enantiomers with the absolute R-configuration (e.g., sotalol) and the aryloxyaminopropanol group includes enantiomers with the S-configuration (e.g., metoprolol, penbutolol, propranolol, timolol, etc.).

It is believed that the more active enantiomer of the β-adrenoblocker binds more efficiently to the receptor under strictly defined stereochemical conditions. Moreover, it is believed that specific functional groups in the blocker molecule play a crucial role in binding to the receptor. We think that the chirality of both the ligand and the receptor should be taken into account in addition to the above consideration.

β-Adrenergic receptors are G-protein coupled receptors, which are integral membrane proteins that contain seven transmembrane domains (transmembrane helices). β-Adrenoreceptors have predominantly α-helical (i.e., right-handed) conformation [139]. The amino acid residues provide specific interactions with the β-blocker molecules but, in our opinion, the chirality of the structures of the receptor is also important. It is not yet unambiguously clear whether the correspondence between the signs of chirality of absolute configurations and optical activity (right-handed α-helices and left-rotating R-enantiomers of the arylaminoethanol group or the more active S-enantiomers of the aryloxyaminopropanol group) is important. This approach to considering the interaction of a chiral drug and a target will help to improve the discovery and development of drugs with a given sign of chirality.

The results in this work can be used to develop a system of correlations between the chiral form of a drug and its effect on a specific molecular target. In the future, this work can help in establishing the nature of the differences in the effects of opposite

enantiomers on a living organism, which, in turn, can be used in the development of medicines.

The phenomenological level of our exploratory research suggests a further understanding of the symmetry foundations of the specific interaction of biomacromolecules. In the future, we will have to elucidate the correspondence between the active forms of chiral drugs and the signs of chirality of biomacromolecule structures of different levels, which are direct targets of drugs or, the structural elements of these macromolecular machines. The data systematized in this article on the sign of chirality for hundreds of drugs make it possible to develop this direction of biophysical pharmacology for more purposeful and successful drug design.

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