

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

**АКТУАЛЬНІ ПИТАННЯ СТВОРЕННЯ
НОВИХ ЛІКАРСЬКИХ ЗАСОБІВ**

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Актуальні питання створення нових лікарських засобів: матеріали XXIX міжнародної науково-практичної конференції молодих вчених та студентів (19-21 квітня 2023 р., м. Харків). – Харків: НФаУ, 2023. – 606 с.

Збірка містить матеріали Всеукраїнської науково-практичної конференції «Youth Pharmacy Science», які представлені за пріоритетними напрямками науково-дослідної роботи Національного фармацевтичного університету. Розглянуто теоретичні та практичні аспекти синтезу біологічно активних сполук і створення на їх основі лікарських субстанцій; стандартизації ліків, фармацевтичного та хіміко-технологічного аналізу; вивчення рослинної сировини та створення фітопрепаратів; сучасної технології ліків та екстемпоральної рецептури; біотехнології у фармації; досягнень сучасної фармацевтичної мікробіології та імунології; доклінічних досліджень нових лікарських засобів; фармацевтичної опіки рецептурних та безрецептурних лікарських препаратів; доказової медицини; сучасної фармакотерапії, соціально-економічних досліджень у фармації, маркетингового менеджменту та фармакоекономіки на етапах створення, реалізації та використання лікарських засобів; управління якістю у галузі створення, виробництва й обігу лікарських засобів; суспільствознавства; фундаментальних та мовних наук.

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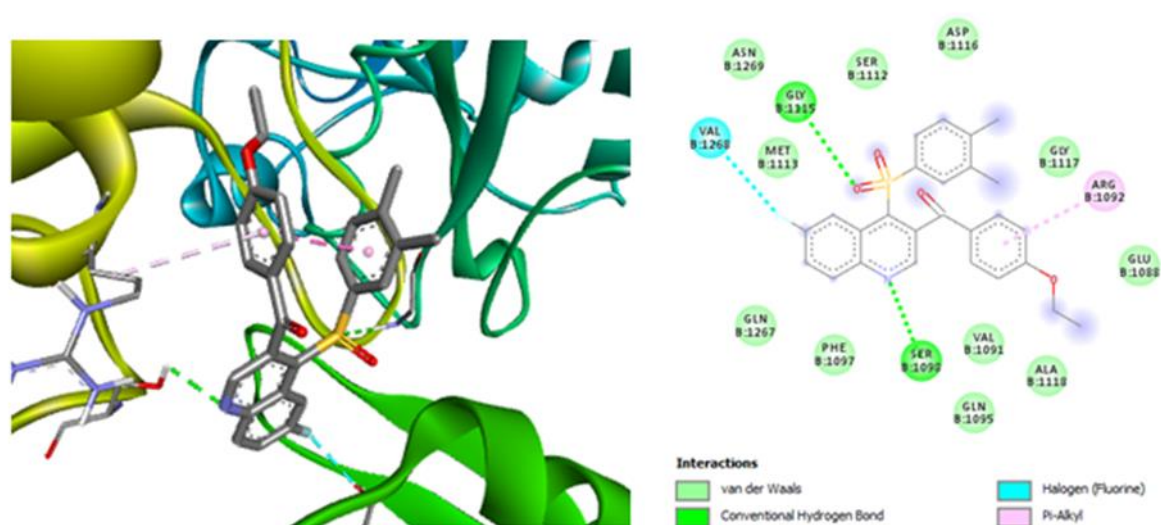


Fig. 2. Visualization of the molecular docking of the leader compound in complex with the DNA gyrase of *Staphylococcus aureus* (PDB ID: 2XCR)

Conclusions. In order to find new molecules with antibacterial action, fluoroquinolone derivatives were generated by modifying the C4 position with a phenylsulfonyl residue and additional modification of the C3 position with aromatic fragments. The results of molecular docking indicate the prospects of such a modification and may be useful in the search for new fluoroquinolone analogs.

ENANTIOMERS: MORE DIFFERENT THAN SIMILAR

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Introduction. The ability of chiral molecules to interact differently with left versus right circularly polarized light is known as optical activity and is one of the most extensively studied activities. It's well-known, that an optically active entity (an enzyme or a receptor) recognizes two enantiomers. It selects the one that fits better and gives a three-point interaction with the ligands. The enantiomer responsible for the biological activity is called the “eutomer”, while the other one, inactive, less active, or even toxic, is referred to as the “distomer”. However, as a rule, the differences in the biological properties of the enantiomers are considered through the prism of pharmacodynamics. At the same time, the influence of chirality on the pharmacokinetics of the molecule is often underestimated.

Aim. Analysis of the effect of chirality of drug molecules on their pharmacodynamics, pharmacokinetics, and toxicity.

Materials and methods. In order to identify the number of chiral substances, which are listed in the European Pharmacopoeia 10.0, the content was analyzed. Based on the data obtained, a literature search and study of individual examples were carried out.

Results and discussion. Based on the literature data, nearly 56 % of the pharmaceuticals marketed and used in therapy are chiral compounds, and, amongst them, 88 % are administered as racemates. Analysis of the content of the European Pharmacopoeia 10.0 showed that the percentage of the chiral substances is higher (over 65 % of 1792 substances analyzed). Moreover, a common phenomenon is the presence of both pure eutomer and racemate at the same time.

It's well-known, that the two enantiomers of a chiral drug may have different pharmacodynamic properties. For instance, (S)-(+)-oxazepam is 100-200 fold more potent than (R)-(-)-oxazepam as a tranquilizer and sedative, (S)-(-)-form of warfarin is more potent as anticoagulant than the (R)-(-) around five times, (S)-(+)-ibuprofen is 100-fold more active enantiomer *in vitro* than (R)-(-)-ibuprofen etc.

However, much less attention is paid to the differences in the pharmacokinetic properties of enantiomers. For example, the (R)-verapamil shows bioavailability more than (S)-verapamil about twice amount, due to reduced hepatic first-pass metabolism, the clearance of (R)-ibuprofen enantiomer is higher than that for (S)-ibuprofen enantiomer, the (R)-form of methadone appears a greater unbound fraction and total renal clearance than (S)-form and so on.

Conclusions. Based on the analysis of the effect of molecule chirality on its pharmacodynamics, pharmacokinetics, and toxicity, we can conclude that it is necessary to consider enantiomers as completely different molecules. The decision to use a single enantiomer versus a mixture of enantiomers of a particular drug should be made based on the data from clinical trials and clinical expertise. The use of the single enantiomer drugs may lead to simpler and more selective pharmacological profiles, improved therapeutic indices, simpler pharmacokinetics, and decreased drug interactions, and requests to determine and control the enantiomeric purity of the enantiomers from a racemic mixture. However, when examining individual examples, it was found that even despite the proven benefits of using optically pure enantiomers, manufacturers continue to develop and market preparations based on racemates.

TESTING OF NEW OXADIAZOLE DERIVATIVES FOR COMPLIANCE WITH LIPINSKI RULES

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Introduction. Computational medicinal chemistry has become an increasingly popular approach to aid in the search for new active pharmaceutical ingredients. This approach uses *in silico* methods to predict the biological activity, physicochemical properties, and potential toxicity of compounds before experimental testing, reducing the time and cost associated with drug discovery. In this thesis, computational medicinal chemistry approaches will be applied to a series of 10 oxadiazole derivatives to identify promising drug candidates for further testing. Calculations of physicochemical and ADMET properties will be conducted to predict the compounds' oral bioavailability. Christopher Lipinski introduced Rule of Five as part of a set of guidelines based on the physicochemical characteristics of substances that are expected to have strong oral bioavailability and permeability. Therefore, these substances are more likely to become successful medications.