

BÖLÜM 10

İLAÇ KEŞFİNDE VERİMLİLİK VE HASSASIYETİ ARTIRMAYA YÖNELİK YENİLİKÇİ STRATEJİLERİ

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GİRİŞ

Medisinal kimya, farmasötik bileşiklerin tasarımı, geliştirilmesi ve optimizasyonuna odaklanan disiplinler arası bir alandır. Kimya, biyoloji ve farmakoloji ilkelerini bir araya getirerek hastalıkları etkili şekilde tedavi edebilecek biyoaktif moleküllerin oluşturulmasını amaçlamaktadır (1). Bu alandaki temel araştırma konuları arasında yeni bileşiklerin sentezi, yapı-aktivite ilişkisi (SAR) çalışmaları, ilaç özelliklerinin (örneğin çözünürlük ve biyoyararlanım) optimizasyonu ve farmakolojik etkilerin değerlendirilmesi yer almaktadır. Küçük moleküllu ilaçların keşfi ve tasarımı, medisinal kimya alanında büyük bir öneme sahip olmuş ve çok sayıda hastalıkla mücadelede yeni tedavilerin geliştirilmesinde temel yapı taşını oluşturmuştur (2). Küçük moleküller, tarihsel olarak kanser, enfeksiyon hastalıkları ve kronik rahatsızlıklar gibi birçok hastalığın etkili tedavisinde kritik bir rol oynamıştır (3-5). Ancak, küçük moleküllu ilaç keşfi süreci çeşitli zorlukları da içerisinde barındırmaktadır. Klinik denemelerde yüksek başarısızlık oranları, biyolojik sistemlerin karmaşıklığı ve hassas hedeflere yönelik tedavilere duyulan ihtiyaç gibi etkenler bu süreci zorlaştırmaktadır (3, 6, 7). Bu nedenle, küçük moleküllu ilaç tasarımının etkinliğini ve başarısını artıracak yenilikçi yaklaşımlara duyulan ihtiyaç giderek artmaktadır (8). Geleneksel yöntemler çoğunlukla deneme-yanılma esasına dayanmakta olup, bu süreç hem zaman alıcı hem de yüksek kaynak tüketimi gerektiren bir yapıya sahiptir. Buna ek olarak, biyolojik sistemlerin karmaşıklığı ve hastalıkların çeşitliliği, ilaç tasarımında daha hedefe yönelik ve stratejik yaklaşımların benimsenmesini zorunlu kılmaktadır. Bu bağlamda, kü-

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KAYNAKLAR

1. Castagnolo, D. Looking Back and Moving Forward in Medicinal Chemistry. *Nature Communications*. 2023;14(1):4299. doi:10.1038/S41467-023-39949-6
2. Campbell, I.B., Macdonald, S. J. F., and Procopiou, P.A. Medicinal Chemistry in Drug Discovery in Big Pharma: Past, Present and Future. *Drug Discovery Today*. 2018;23(2):219–34. doi: 10.1016/j.drudis.2017.10.007.
3. Zhong, L., Li, Y., Xiong, L. et al. Small Molecules in Targeted Cancer Therapy: Advances, Challenges, and Future Perspectives. *Signal Transduction and Targeted Therapy*. 2021;2021 6:1 6(1):1-48. doi:10.1038/s41392-021-00572-w.
4. Davis, J. S., Ferreira, D., Paige, E. et al. Infectious Complications of Biological and Small Molecule Targeted Immunomodulatory Therapies. *Clinical Microbiology Reviews*. 2020;33(3):1–117. doi: 10.1128/CMR.00035-19.
5. Parra Sánchez, A.R., Voskuyl, A. E., and van Vollenhoven, R. F. Treat-to-Target in Systemic Lupus Erythematosus: Advancing towards Its Implementation. *Nature Reviews Rheumatology*. 2022;18(3):146-57. doi:10.1038/S41584-021-00739-3
6. Bedard, Philippe L., Hyman, David M., Davids, Matthew S., et al. Small Molecules, Big Impact: 20 Years of Targeted Therapy in Oncology. *The Lancet*. 2020;395(10229):1078–88. doi: 10.1016/S0140-6736(20)30164-1.
7. Keserü, G. M., and Makara, G. M. The Influence of Lead Discovery Strategies on the Properties of Drug Candidates. *Nature Reviews Drug Discovery*. 2009;8(3):203–12. doi:10.1038/nrd2796
8. Saldívar-González, F.I., and Medina-Franco, J.L. Approaches for Enhancing the Analysis of Chemical Space for Drug Discovery. *Expert Opinion on Drug Discovery*. 2022;17(7):789-98. doi: 10.1080/17460441.2022.2084608
9. Zhao, R., Zhu, J., Jiang, X., and Bai, R. Click chemistry-aided drug discovery: a retrospective and prospective outlook. *European Journal of Medicinal Chemistry*. 2024;264: 116037. doi:10.1016/j.ejmech.2023.116037
10. Wells, J. A., and Kumru, K. (2024). Extracellular targeted protein degradation: an emerging modality for drug discovery. *Nature Reviews Drug Discovery*. 2024;23: 126-140. doi:10.1038/s41573-023-00833-z
11. Peterson, A. A., and Liu, D. R. Small-molecule discovery through DNA encoded libraries. *Nature Reviews Drug Discovery*. 2023;22: 699-722. doi:10.1038/s41573-023-00713-6
12. Sadybekov, A. V., and Katritch, V. Computational approaches streamlining drug discovery. 2023; *Nature*, 616: 673–685. doi:10.1038/s41586-023-05905-z
13. Giordano, D., Biancaniello, C., Argenio, M. A., and Facchiano, A. Drug design by pharmacophore and virtual screening approach. *Pharmacy (Basel)*. 2022;15: 646. doi:10.3390/ph15050646
14. Kolb, H. C., Finn, M. G., and Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angewandte Chemie International Edition*. 2001;40(11):2004–21. doi:10.1002/1521-3773(20010601)40:11<2004::aid-anie2004>3.0.co;2-5.
15. Caselli, E., Romagnoli, C., Vahabi, R. et al. Click Chemistry in Lead Optimization of Boronic Acids as β -Lactamase Inhibitors. *Journal of Medicinal Chemistry*. 2015; 58(14):5445–58. doi: 10.1021/acs.jmedchem.5b00341
16. Le Droumaguet, B., Guerrouache, M., and Carbonnier, B. Contribution of the “Click Chemistry” Toolbox for the Design, Synthesis, and Resulting Applications of Innovative and Efficient Separative Supports: Time for Assessment. *Macromolecular Rapid Communications*. 2022;43(19):2200210. doi.org/10.1002/marc.202200210
17. Ellis, R. John. (2001). Macromolecular Crowding: Obvious but Underappreciated. *Trends in Biochemical Sciences*, 26(10):597-604. doi:10.1016/S0968-0004(01)01938-7.
18. Shankaraiah, N., Sakla, A.P., Laxmikeshav, K., et al. Reliability of Click Chemistry on Drug Discovery: A Personal Account. *The Chemical Record*. 2020;20(4):253-72. doi:10.1002/tcr.201900027.
19. Wurz, R. P., Dellamaggiore, K., Dou, H. et al. A “Click Chemistry Platform” for the Rapid

- Synthesis of Bispecific Molecules for Inducing Protein Degradation. *Journal of Medicinal Chemistry*. 2018;61(2):453–61. doi: 10.1021/acs.jmedchem.6b01781
20. Glassford, I., Teijaro, C. N., Daher, S. S. et al. Ribosome-Templated Azide-Alkyne Cycloadditions: Synthesis of Potent Macrolide Antibiotics by in Situ Click Chemistry. *Journal of the American Chemical Society*. 2016;138(9):3136–44. doi: 10.1021/jacs.5b13008.
21. Kugler, M., Hadzima, M., Dzijak, R. et al. Identification of Specific Carbonic Anhydrase Inhibitors via in Situ Click Chemistry, Phage-Display and Synthetic Peptide Libraries: Comparison of the Methods and Structural Study. *RSC Medicinal Chemistry*. 2023;14(1):144–53. doi:10.1039/D2MD00330A.
22. Cai, J. H., Zhu, X.Z, Guo, P.Y. et al. Recent Updates in Click and Computational Chemistry for Drug Discovery and Development. *Frontiers in Chemistry*. 2023;11:1114970. doi: 10.3389/fchem.2023.1114970.
23. Barrow, A. S., Smedley, C. J., Zheng, Q., et al. (2019). The Growing Applications of SuFEx Click Chemistry. *Chemical Society Reviews*. 2019;48(17):4731–58. doi:10.1039/C8CS00960K.
24. Bhardwaj, A., Kaur, J., Wuest, M et al. In Situ Click Chemistry Generation of Cyclooxygenase-2 Inhibitors. *Nature Communications*. 2017;8(1):1–14. doi:10.1038/S41467-016-0009-6
25. Hu, X., and Manetsch, R. Kinetic Target-Guided Synthesis. *Chemical Society Reviews*. 2010;39(4):1316–24. doi:10.1039/B904092G.
26. Rzuczek, S. G., Park, H., and Disney, M.D. A Toxic RNA Catalyzes the In Cellulo Synthesis of Its Own Inhibitor. *Angewandte Chemie International Edition*. 2014;53(41):10956–59. doi:10.1002/anie.201406465.
27. Wang, X., Huang, B., Liu, X. et al. Discovery of Bioactive Molecules from CuAAC Click-Chemistry-Based Combinatorial Libraries. *Drug Discovery Today*. 2016;21(1):118–32. doi:10.1016/j.drudis.2015.08.004.
28. Kim, E., and Koo, H. Biomedical Applications of Copper-Free Click Chemistry: In Vitro, in Vivo, and Ex Vivo. *Chemical Science*. 2019;10(34):7835–51. doi:10.1039/c9sc03368h.
29. Zhao, L., Zhao, J., Zhong, K. et al. Targeted Protein Degradation: Mechanisms, Strategies and Application. *Signal Transduction and Targeted Therapy*. 2022;2022 7:1 7(1):1–13. doi:10.1038/s41392-022-00966-4.
30. Bondeson, Daniel P., Mares, A., Smith, Ian E. D. et al. Catalytic in Vivo Protein Knockdown by Small-Molecule PROTACs. *Nature Chemical Biology*. 2015;11(8):611–17. doi:10.1038/nchembio.1858.
31. Zhang, C., Liu, Y., Li, G. et al. Targeting the Undruggables—the Power of Protein Degraders. *Science Bulletin*. 2024; 69(11):1776–97. doi:10.1016/j.scib.2024.03.056.
32. Ding, Y., Fei, Y., and Lu, B. Emerging New Concepts of Degradation Technologies. *Trends in Pharmacological Sciences*. 2020;41(7):464–74. doi: 10.1016/j.tips.2020.04.005
33. Eldridge, A.G., and O'Brien, T. Therapeutic Strategies within the Ubiquitin Proteasome System. *Cell Death and Differentiation*. 2010;17(1):4–13. doi: 10.1038/cdd.2009.82.
34. Chen, Y. J., Wu, H., and Shen X. Z. The Ubiquitin–Proteasome System and Its Potential Application in Hepatocellular Carcinoma Therapy. *Cancer Letters*. 2016;379(2):245–52. doi:10.1016/j.canlet.2015.06.023.
35. Saftig, P., and Klumperman, J. Lysosome Biogenesis and Lysosomal Membrane Proteins: Trafficking Meets Function. *Nature Reviews Molecular Cell Biology*, 2009;10:9 10(9):623–35. doi:10.1038/nrm2745.
36. Matsuo, B., Granados, A., Levitre, G., et al. Photochemical Methods Applied to DNA Encoded Library (DEL) Synthesis. *Accounts of Chemical Research*. 2023;56(3):385–401. doi: 10.1021/acs.accounts.2c00778
37. Clark, M. A., Acharya, R. A., Arico-Muendel, C. C. et al. Design, Synthesis and Selection of DNA-Encoded Small-Molecule Libraries. *Nature Chemical Biology*. 2009;5(9):647–54. doi:10.1038/nchembio.211;kwrd=chemistry.
38. Gartner, Z. J., and Liu., D. R. The Generality of DNA-Templated Synthesis as a Basis for Evolving Non-Natural Small Molecules. *Journal of the American Chemical Society*. 2001;123(28):6961–

63. doi: 10.1021/ja015873n.
39. Brenner, S., and Lerner. R. Encoded Combinatorial Chemistry. *Proceedings of the National Academy of Sciences*. 1992;89(12):5381–83. doi:10.1073/PNAS.89.12.5381.
40. Neri, D., and Lerner, R.A. DNA-Encoded Chemical Libraries: A Selection System Based on Endowing Organic Compounds with Amplifiable Information. *Annual Review of Biochemistry*. 2018;87:479–502. doi: 10.1146/annurev-biochem-062917-012550
41. Scheuermann, J., Dumelin, C. E., Melkko, S. et al. DNA-Encoded Chemical Libraries. *Journal of Biotechnology*. 2006;126(4):568–81. doi:10.1016/j.jbiotec.2006.05.018.
42. Ferreira, LLG., Andricopulo, A.D. ADMET Modeling Approaches in Drug Discovery. *Drug Discovery Today*. 2019;24(5):1157–1165. doi.org/10.1016/j.drudis.2019.03.015
43. Cochrane, W. G., Fitzgerald, P. R., and Paegel, B. M. Antibacterial Discovery via Phenotypic DNA-Encoded Library Screening. *ACS Chemical Biology*. 2021;16(12):2752–56. doi.org/10.1021/acscchembio.1c00714
44. Harris, P. A., Berger, S. C., Jeong, J. U. et al. Discovery of a First-in-Class Receptor Interacting Protein 1 (RIP1) Kinase Specific Clinical Candidate (GSK2982772) for the Treatment of Inflammatory Diseases. *Journal of Medicinal Chemistry*. 2017;60(4):1247–61. doi.org/10.1021/acs.jmedchem.6b01751.
45. Chen, Q., Li, Y., Lin, C., et al. Expanding the DNA-Encoded Library Toolbox: Identifying Small Molecules Targeting RNA. *Nucleic Acids Research*. 2022;50(12):e67–e67. doi:10.1093/nar/gkac173.
46. Ellis, R. John. Macromolecular Crowding: Obvious but Underappreciated. *Trends in Biochemical Sciences*. 2001; 26(10):597–604. doi:10.1016/S0968-0004(01)01938-7.
47. Petersen, L.K., Christensen, A.B., Andersen, J., et al. Screening of DNA-Encoded Small Molecule Libraries inside a Living Cell. *Journal of the American Chemical Society*. 2021;143(7):2751–56. doi: 10.1021/jacs.0c09213
48. Wichert M., Guasch, L., M. Franzini, R.M Challenges and Prospects of DNA-Encoded Library Data Interpretation. *Chemical Reviews*. 2024;124 (22): 12551-12572. doi:10.1021/acs.chemrev.4c00284
49. Hsieh, J. C., Giannakoulis, S., Petersson, J. E. et al. Computational Chemistry for the Identification of Lead Compounds for Radiotracer Development. *Pharmaceuticals*. 2023;16(2):317. doi:10.3390/ph16020317/s1.
50. Rusinko, A., Rezaei, M., Friedrich, L. et al. AIDDISON: Empowering Drug Discovery with AI/ML and CADD Tools in a Secure, Web-Based SaaS Platform. *Journal of Chemical Information and Modeling*. 2024;64(1):3–8. doi: 10.1021/acs.jcim.3c01016
51. McNair, D. Artificial Intelligence and Machine Learning for Lead-to-Candidate Decision-Making and Beyond. *Annual Review of Pharmacology and Toxicology*. 2023;63:77–97. doi:10.1146/annurev-pharmtox-051921-023255
52. Liu, G., Catacutan, D. B., Rathod, K. et al. Deep Learning-Guided Discovery of an Antibiotic Targeting *Acinetobacter Baumannii*. *Nature Chemical Biology*. 2023;19(11):1342–50. doi:10.1038/s41589-023-01349-8.
53. Zhang, X., Zhang, O., Shen, C. et al. Efficient and Accurate Large Library Ligand Docking with KarmaDock. *Nature Computational Science*. 2023;3(9):789–804. doi: 10.1038/s43588-023-00511-5.
54. Lima, A. N., Philot, E. A., Trossini, G. H. G. et al. Use of Machine Learning Approaches for Novel Drug Discovery. *Expert Opinion on Drug Discovery*. 2016;11(3):225–39. doi:10.1517/17460441.2016.1146250.
55. Macalino, S. J. Y., Gosu, V., Hong, S. et al. Role of Computer-Aided Drug Design in Modern Drug Discovery. *Archives of Pharmacal Research*. 2015;38:9 38(9):1686–1701. doi:10.1007/S12272-015-0640-5.
56. Maia, E. H. B., Assis, L.C., Oliveira, T. A., et al. Structure-Based Virtual Screening: From Classical to Artificial Intelligence. *Frontiers in Chemistry*. 2020;8:481382. doi:10.3389/fchem.2020.00343/xml/nlm.

57. Defelipe, L.A., Arcon, J. P., Modenutti, C. P. et al. Solvents to Fragments to Drugs: MD Applications in Drug Design. *Molecules*. 2018;23(12):3269. doi:10.3390/molecules23123269.
58. Keutzer, L., You, H., Farnoud, A., et al. Machine Learning and Pharmacometrics for Prediction of Pharmacokinetic Data: Differences, Similarities and Challenges Illustrated with Rifampicin. *Pharmaceutics*. 2022;14(8), 1530. 10.3390/pharmaceutics14081530
59. Zhu, L., Chen, X., Abola, E. E. et al. Serial Crystallography for Structure-Based Drug Discovery. *Trends in Pharmacological Sciences*. 2020;41(11):830–39. doi: 10.1016/j.tips.2020.08.009
60. Protein Data Bank (<http://rcsb.org>)
61. Lionta, E., Spyrou, G., Vassilatis, D. K. et al. Structure-Based Virtual Screening for Drug Discovery: Principles, Applications and Recent Advances. *Current Topics in Medicinal Chemistry*. 2014;14(16):1923–38. doi:10.2174/1568026614666140929124445.
62. Forli, S., Huey, R., Pique, M. E. et al. Computational Protein–Ligand Docking and Virtual Drug Screening with the AutoDock Suite. *Nature Protocols*. 2016;11(5):905–19. doi:10.1038/nprot.2016.051.
63. Shen, C., Wang, Z., Yao, X. et.al. Comprehensive Assessment of Nine Docking Programs on Type II Kinase Inhibitors: Prediction Accuracy of Sampling Power, Scoring Power and Screening Power. *Briefings in Bioinformatics*. 2020;21(1):282–97. doi:10.1093/bib/bby103.
64. Cheng, T., Li, Q., Zhou, Z. et al. Structure-Based Virtual Screening for Drug Discovery: A Problem-Centric Review. *AAPS Journal*. 2012;14(1):133–41. doi:10.1208/s12248-012-9322-0/met-rics.
65. van Montfort, R. L. M., and Workman, P. Structure-Based Design of Molecular Cancer Therapeutics. *Trends in Biotechnology*. 2009;27(5):315–28. doi: 10.1016/j.tibtech.2009.02.003
66. Liu, X., Shi, D., Zhou, S., et al. Molecular Dynamics Simulations and Novel Drug Discovery. *Expert Opinion on Drug Discovery*. 2018;13(1):23–37. doi: 10.1080/17460441.2018.1403419.
67. Kuzmanic, A., Bowman, G. R., Juarez-Jimenez, J. et al. Investigating Cryptic Binding Sites by Molecular Dynamics Simulations. *Accounts of Chemical Research*. 2020;53(3):654–61. doi: 10.1021/acs.accounts.9b00613
68. Yelshanskaya, M.V., Singh, A. K., Narangoda, C. et al. Structural Basis of AMPA Receptor Inhibition by Trans-4-Butylcyclohexane Carboxylic Acid. *British Journal of Pharmacology*. 2022;179(14):3628–44. doi:10.1111/bph.15254.
69. Wu, H., Liu, J., Zhang, R. et al. A Review of Deep Learning Methods for Ligand Based Drug Virtual Screening. *Fundamental Research*. 2024;4(4):715–37. doi:10.1016/j.fmre.2024.02.011.
70. Bonanno, Etienne, and Jean Paul Ebejer, J.P. Applying Machine Learning to Ultrafast Shape Recognition in Ligand-Based Virtual Screening. *Frontiers in Pharmacology*. 2020;10:501024. doi.org/10.3389/fphar.2019.01675
71. Lee, C.H., Huang, H. C., and Juan, H. F. Reviewing Ligand-Based Rational Drug Design: The Search for an ATP Synthase Inhibitor. *International Journal of Molecular Sciences*. 2011;12(8):5304–18. doi:10.3390/IJMS12085304.
72. Yang, X., Wang, Y., Byrne, R. et al. Concepts of Artificial Intelligence for Computer-Assisted Drug Discovery. *Chemical Reviews*. 2019;119(18):10520–94. doi: 10.1021/acs.chemrev.8b00728
73. Vyas, V. K., Bhati, S., Patel, S. et al. Structure- and Ligand-Based Drug Design Methods for the Modeling of Antimalarial Agents: A Review of Updates from 2012 Onwards. *Journal of Biomolecular Structure and Dynamics*. 2022;40(20):10481–506. doi:10.1080/07391102.2021.1932598
74. Tang, Y., Feng, B., Wang, Y., et. al. Structure-Based Discovery of CZL80, a Caspase-1 Inhibitor with Therapeutic Potential for Febrile Seizures and Later Enhanced Epileptogenic Susceptibility. *British Journal of Pharmacology*. 2020; 77(15):3519–34. doi:10.1111/bph.15076.
75. Sainy, J., and Sharma, R. QSAR Analysis of Thiolactone Derivatives Using HQSAR, CoMFA and CoMSIA. SAR and QSAR in Environmental Research. 2015;26(10):873–92. doi: 10.1080/1062936X.2015.1095238
76. Yang, Z.Y., Fu, L., Lu, A. P. et al. Semi-Automated Workflow for Molecular Pair Analysis and QSAR-Assisted Transformation Space Expansion. *Journal of Cheminformatics*. 2021;13(1):1–

14. doi:10.1186/s13321-021-00564-6/tables/5.
77. van Drie, J. H. Pharmacophore Discovery - Lessons Learned. *Current Pharmaceutical Design*. 2005;9(20):1649–64. doi:10.2174/1381612033454568.
78. Atz, K., Cotos, L., Isert, C., et al. Prospective de Novo Drug Design with Deep Interactome Learning. *Nature Communication*. 2024;15(1):3408. doi: 10.1038/s41467-024-47613-w
79. Thomas, M., Smith, R.T., O'Boyle, N.M. et al. Comparison of Structure-and Ligand-Based Scoring Functions for Deep Generative Models: A GPCR Case Study. *Journal of Cheminformatics*. 2021;13(39). doi: 10.1186/s13321-021-00516-0
80. Schneider, G. Future de Novo Drug Design. *Molecular Informatics*. 2014;33(6-7):397–402. doi:10.1002/minf.201400034.
81. Schneider, G., Funatsu, K., Okuno, Y. et al. De Novo Drug Design – Ye Olde Scoring Problem Revisited. *Molecular Informatics*. 2017;36(1-2). doi: 10.1002/minf.201681031
82. He, H., Duo, H., Hao, Y. et al. Computational Drug Repurposing by Exploiting Large-Scale Gene Expression Data: Strategy, Methods and Applications. *Computers in Biology and Medicine*. 2023;155:106671. doi: 10.1016/j.compbiomed.2023.106671.
83. Haupt, VJ, Schroeder, M. Old Friends in New Guise: Repositioning of Known Drugs with Structural Bioinformatics. *Briefings in Bioinformatics*. 2011;12(4):312-26. doi: 10.1093/bib/bbr011.
84. Keiser, M. J, Setola, V., Irwin, J. J. et al. C. Predicting New Molecular Targets for Known Drugs, *Nature*. 2009;12;462(7270):175-81. doi: 10.1038/nature08506
85. Yi, J., Shi, S., Fu, L. et al. (2024). OptADMET: A Web-Based Tool for Substructure Modifications to Improve ADMET Properties of Lead Compounds. *Nature Protocols*. 2024;19(4):1105-1121. doi: 10.1038/s41596-023-00942-4
86. Daina, A., Michielin, O., Zoete, V. Scientific reports, and undefined 2017. SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules. *Scientific Reports*. 2017;7:42717 | DOI: 10.1038/srep42717
87. Sohlenius-Sternbeck, A.K., Terelius, Y. Evaluation of ADMET Predictor in Early Discovery Drug Metabolism and Pharmacokinetics Project Work. *Drug Metabolism and Disposition*. 2022;50(2):95-104. doi: 10.1124/dmd.121.000552.
88. Fu, L., Shi, S., Yi, J. et al. ADMETlab 3.0: An Updated Comprehensive Online ADMET Prediction Platform Enhanced with Broader Coverage, Improved Performance, API Functionality and Decision. *Nucleic Acids Research*. 2024;52:422-31. doi:10.1093/nar/gkae236.
89. Morgan, P., Van Der Graaf, P.H., Arrowsmith, J. Can the Flow of Medicines Be Improved? Fundamental Pharmacokinetic and Pharmacological Principles toward Improving Phase II Survival. *Drug Discovery Today*. 2012;17(9-10):419-24. doi: 10.1016/j.drudis.2011.12.020
90. Medina-Franco, J.L Grand Challenges of Computer-Aided Drug Design: The Road Ahead. *Frontiers in Drug Discovery*. 2021;1: 728551. doi:10.3389/fddsv.2021.728551