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ILMIY AXBOROTNOMA

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Obuna indeksi – yakka tartibdagi obunachilar uchun **- 5583,**
tashkilot, korxonalar uchun **- 5584**

M U N D A R I J A
C O N T E N T S

№	Maqola nomi	Article title	Bet/ page
1.	Yuqori chastotali II-turdagi radio portlash spektral kuzatuvlaridan foydalanib magnit maydon kuchini baholash **Pulatov D., Mirtoshev Z.**	Estimation Of The Coronal Magnetic Field Strength Using High-Frequency Type Ii Radio Burst Observations **Pulatov D., Mirtoshev Z.**	**5-11**
2.	Rayxon (OCIMUM) o‘simligi efir moyi kimyoviy tarkibiga iqlim omillarining ta’sirini GX–MS usulida tadqiq etish **Siddikova Y., Saifullaeva Sh., Mukhamadiyev A., N.Fazlieva, Nayimova B., Muhamadiyev N.**	Study of the influence of climate factors on the chemical composition of basil (ocimum) essential oil using the GH–MS method **Siddikova Y., Saifullaeva Sh., Mukhamadiev A., N.Fazlieva, Nayimova B., Muhamadiev N.**	**12-20**
3.	Bentonitni montmorillonit bilan boyitishning samarali usullari va termal ishlov berishning kation almashinuvi quvvatiga ta'siri **Mamadoliev I., Abdikamalova A., Ruzieva S.**	Effective methods for bentonite enrichment with montmorillonite and the impact of thermal treatment on cation exchange capacity **Mamadoliev I., Abdikamalova A., Ruzieva S.**	**21-28**
4.	$KPbBr_3$ asosidagi peroled tuzilmalarida zaryad tashish mexanizmlari va energetik sathlarning moslashuvi **Rahmonova M., Muxamadiyev N.**	Charge transport mechanisms and energy level alignment in $KPbBr_3$ -based peroled structures **Rahmonova M., Mukhamadiev N.**	**29-36**
5.	*N*-(4-(((7-Nitroxinazolin-4-il) amino) metil)fenil) siklogeksankarboksamid sintezi **Gaybullaev Sh., Takhirov Y., Chao Niu, Bozorov Kh.**	Synthesis of N-(4-(((7-nitroquinazolin-4-YL) amino) methyl) phenyl) cyclohexanecarboxamide **Gaybullaev Sh., Takhirov Y., Chao Niu, Bozorov Kh.**	**37-41**
6.	3-brom-pirido[2,3-*d*]pirimidinonlarning sintezi **Khushnazarov Z., Turgunov D., Bozorov Kh.**	synthesis of 3-bromo-pyrido[2,3-d]pyrimidinones **Khushnazarov Z., Turgunov D., Bozorov Kh.**	**42-46**
7.	Zarrachalar tezlatkichlarida materiallarning aktivatsiyasi va radiatsion xavflar **Temirov J., Khasanov Sh., Safarov A., Karimberganova Q.**	Material activation and radiological hazards in particle accelerators **Temirov J., Khasanov Sh., Safarov A., Karimberganova Q.**	**47-57**
8.	Geoinformatsion dasturlar yordamida demografik atlaslar yaratishning afzalliklariga nazar **Tukhtamishev Sh., Khudoyarova Sh., Shirinboyev D.**	Advantages of creating demographic atlases using geoinformation software **Tukhtamishev Sh., Khudoyarova Sh., Shirinboev D.**	**58-62**
9.	Siklopropilatsetilen asosida atsetilen spirtlari sintezi, ularning nazariy energetik xarakteristikalari va nadfoksidaza oqsili (7U8G) bilan molekulyar birikish tahlili **Ziyadullaev M.E., Nurmanov S.E., Buriev F.Kh., Abdukhalikov F.J.**	Synthesis of acetylenic alcohols based on cyclopropylacetylene, their theoretical energetic characterization, and molecular docking analysis with nadph oxidase (7U8G) protein **Ziyadullaev M.E., Nurmanov S.E., Buriev F.Kh., Abdukhalikov F.J.**	**63-71**
10.	Tetratsiklik tieno[3,2-*d*]pirimidinonlarning siklooksigenaza-2 ingibitorlari sifatida *in silico* tadqiqi **Nasrullaev A., Buronov A., Gaybullaev Sh., Bozorov Kh.**	In silico evaluation of tetracyclic thieno[3,2-d]pyrimidinones as potential cyclooxygenase-2 inhibitors **Nasrullaev A., Buronov A., Gaybullaev Sh., Bozorov Kh.**	**72-76**
11.	H3PO4, KOH va ZnCl2 yordamida olingan faollashtirilgan ko‘mirning morfologik va strukturaviy xususiyatlarining qiyosiy tahlili **Ergasheva D., Mukhamadiyev A., Mukhamadiyev N., Uzokov J.**	Comparative analysis of the morphological and structural properties of activated carbon prepared using H_3PO_4, KOH, and $ZnCl_2$ **Ergasheva D., Mukhamadiev A., Mukhamadiev N., Uzokov J.**	**77-81**
12.	CO_2 NI quyosh nuri ta’sirida samarali konversiyalashni ta’minlovchi g-C_3N_4/$CoNi_2S_4$ geterotuzilmali nanomateriallar sintezi va fizik-kimyoviy xossalari **Samiev A., Nizamov U.N., Mirzaev Sh., Ruzimuradov O., Nasimov A.**	Synthesis and physicochemical properties of γ-C3N4/CoNi2S4 heterostructured anomaterials providing efficient conversion of CO2 under the influence of sunlight **Samiev A., Nizamov U.N., Mirzaev Sh., Ruzimuradov O., Nasimov A.**	**82-87**

№	Maqola nomi	Article title	Bet/ page
13.	Atrof muhitdagi ammiak mikrokensentratsiyasini monigitori uchun gibrid perovskit $MA_xFA_{1-x}PbI_3$ fluoressent sensori tayyorlash **Eshmuradova G.B., Tashpulatov Kh.Sh., Khursandov J.M., Normuradov O.U., Norboyev Q.M., Toshpulatov D.T.**	Preparation of hybride perovskite $MA_xFA_{1-x}PbI_3$-fluorescent sensor for the monitoring of ammonia microconcentration in environment **Eshmuradova G.B., Tashpulatov Kh.Sh., Khursandov J.M., Normuradov O.U., Norboev Q.M., Toshpulatov D.T.**	**88-92**
14.	Al^{3+} bilan modifikatsiyalangan shpinel tuzilishga ega $Li_{1.33}Al_XMn_{1.67-X}O_4$ ($0 \leq x < 0.7$) tarkibli adsorbentlarning zol-gel sintezi va fizik-kimyoviy xossalari **Begimkulova Sh.A., Nematova Sh.Sh., Baxriev I.S., Mirzaev Sh.E., Ruzimuradov O.N., Nasimov A.M.**	Sol-gel synthesis and physicochemical properties of adsorbents consisting of Al^{3+} modified spinel structure $LI_{1.33}Al_XMn_{1.67-X}O_4$ ($0 \leq X < 0.7$) **Begimkulova Sh.A., Nematova Sh.Sh., Baxriev I.S., Mirzaev Sh.E., Ruzimuradov O.N., Nasimov A.M.**	**93-99**
15.	CdCr2Se4 va CuCr4Se4 magnitli yarimo‘tkazgichda magnit-optik effektlar **Dosmurodov G.**, **Kurbaniyazov A.**, **Boboqambarova G.**	Magneto-optical effects in the magnetic semiconductor CdCr2Se4 AND CuCr4Se4 **Dosmurodov G.**, **Kurbaniyazov A.**, **Bobokambarova G.**	**100-104**
16.	Sophora lehmanni va Cicer mogoltavikum o‘simliklari yer ustki qismilarining flavonoidlari **Gafurov A.Zh, Botirov E. Kh.**	Flavonoids of aerial parts of sophora lehmannii and cicer mogoltavicum **Gafurov A.Zh, Botirov E. Kh.**	**105-109**
17.	Buxoro viloyatining balneologik resurslari va ularning aholi salomatligini yaxshilashdagi ahamiyati **Zaynutdinova D.K., Nematova Kh. Kh.**	Balneological resources of the bukhara region and their significance in improving public health **Zaynutdinova D.K., Nematova Kh. Kh.**	**110-116**
18.	Tabiiy cho‘kuvchan gruntlarni polimer-kompozitsion eritmalar bilan inyeksion mustahkamlash texnologiyasini matematik rejalashtirish **Bakhriyev N.F., Kholiqulov O.O., Nurmatova R.K.**	Mathematical planning of injection strengthening technology of natural collapsible soils using polymer-composite solutions **Bakhriyev N.F., Kholikulov O.O., Nurmatova R.K.**	**117-125**
19.	Adgezion kontaktlarda ishqalanish koeffitsiyentiga geometrik parametrlar hamda tashqi yuk ta’sirining tahlili **Bekmamatova G., Xoliqulov O., Tojinorov M.**	Analysis of geometric parameters and external load on the friction coefficient in adhesive contacts **Bekmamatova G., Xolikulov O., Tojinorov M.**	**126-131**
20.	Markaziy Osiyo iqlim sharoitida sorbsion sovutgichlardan biogaz komplekslari bilan simbiozda foydalanish istiqbollari **Abdusamiyev F., Bahriev S., Sattarov S.**	Prospects for using sorption refrigerators in symbiosis with biogas complexes in the climatic conditions of Central Asia **Abdusamiev F., Bahriev S., Sattarov S.**	**132-136**
21.	Maple tizimida algebraik ko’pxilliklarni ratsional parametrlashining nazariy asoslari va kompyuterda amalga oshirilishi **Usmonova N.**	Theoretical foundations and computer implementation of rational parameterization of algebraic manifolds in the maple system **Usmonova N.**	**137-142**
22.	$Fe_5Ga_6Gd_2YZr$ ko‘p komponentli kristallining element tarkibi va tebranish xossalarini rentgen-fluoresans (XRF) va raman spektroskopiyasi yordamida tadqiq etish **Nasirova N., Fayziyev Sh., Saidov Q., Qaxorova Sh., Sharipov M., Djuraev D.**	Investigation of the elemental composition and vibrational properties of the multicomponent crystal Fe5Ga6Gd2YZr using X-RAY fluorescence (XRF) and raman spectroscopy **Nasirova N., Fayziyev Sh., Saidov Q., Qaxorova Sh., Sharipov M., Djuraev D.**	**143-152**
23.	Xofp tipidagi tenglamalar sistemasi uchun Koshi masalasi **Erkinova D. A.**, **Imomnazarov Kh. Kh.**	Cauchy problem for a Hopf-type system **Erkinova D. A.**, **Imomnazarov Kh. Kh.**	**153-157**
24.	Ar va HCl izotopologlari o‘rtasida hosil bo‘lgan komplekslarning kvant-kimyoviy tahlili: AIM, RDG va NCI usullari yordamida solvatatsiya effektlarini o‘rganish **Khujamov U.**	Quantum-chemical analysis of complexes formed between Ar and HCL isotopologues: studying solvation effects using AIM, RDG, and NCI methods **Khujamov U.**	**158-167**

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IN SILICO EVALUATION OF TETRACYCLIC THIENO[3,2-d]PYRIMIDINONES AS POTENTIAL CYCLOOXYGENASE-2 INHIBITORS

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Abstract. In the present study, a series of tetracyclic thieno[3,2-*d*]pyrimidin derivatives were subjected to molecular docking simulations to evaluate their binding affinity toward the cyclooxygenase-2 (COX-2) active site. Docking results revealed several promising compounds exhibiting stable binding conformations and favorable interactions, including hydrogen bonds, hydrophobic contacts, and π–π stacking with key amino acid residues within the catalytic pocket. Notably, the highest-ranking derivatives formed crucial interactions with COX-2, suggesting their potential as selective inhibitors. These findings highlight the tetracyclic thieno[3,2-*d*]pyrimidine scaffold as a valuable platform for the rational design and optimization of novel COX-2 inhibitors.

Keywords: drug design, target, cyclooxygenase, thieno[3,2-*d*]pyrimidines, molecular docking, hydrogen bonds.

Tetratsiklik tieno[3,2-*d*]pirimidinonlarning siklooksigenaza-2 ingibitorlari sifatida *in silico* tadqiqi

Annotatsiya. Mazkur ishda tetratsiklik thieno[3,2-*d*]pirimidin hosilalari molekulyar doking orqali siklooksigenaza-2 (COX-2) faol markaziga bog‘lanish qobiliyati bo‘yicha o‘rganildi. Doking natijalari bir nechta istiqbolli birikmalarni aniqladi, ular katalitik bo‘shliqdagi kalit aminokislota qoldiqlari bilan vodorod bog‘lari, gidrofobik ta’sirlar va π–π stacking kabi barqaror o‘zaro ta’sirlarni hosil qildi. Eng yuqori docking ballga ega birikmalar COX-2 bilan muhim bog‘lanishlarni o‘rnatganligi qayd etildi, bu ularning selektiv ingibitorlik salohiyatini ko‘rsatadi. Ushbu natijalar tetratsiklik thieno[3,2-*d*]pirimidin yadrosini yangi COX-2 inhibitorlarini dizayn qilish va optimallashtirish uchun samarali platforma sifatida ajratib turadi.

Kalit so‘zlar: dori vositalarini dizayni, nishon, siklooksigenaza, thieno[3,2-*d*]pirimidinlar, molekulyar doking, vodorod bog‘lari.

In silico исследование тетрациклических тиено[3,2-*d*]пиримидинонов в качестве потенциальных ингибиторов циклооксигеназы-2

Аннотация. В настоящем исследовании был проведен молекулярный докинг серии тетрациркулярных производных тиено[3,2-*d*]пиримидина с целью оценки их сродства к активному центру циклооксигеназы-2 (COX-2). Результаты докинга выявили несколько перспективных соединений, демонстрирующих стабильные конформации связывания и благоприятные взаимодействия, включая водородные связи, гидрофобные контакты и π–π stacking с ключевыми

аминокислотными остатками каталитического кармана. Наиболее высоко оцененные производные установили критические взаимодействия с COX-2, что указывает на их потенциал в качестве селективных ингибиторов. Эти результаты подчеркивают, что тетрациркулярный тиено[3,2-*d*]пиримидиновый каркас является ценным основанием для рационального дизайна и оптимизации новых COX-2 ингибиторов.

Ключевые слова: разработка лекарственных средств, мишень, циклооксигеназа, тиено[3,2-*d*]пиримидины, молекулярный докинг, водородные связи.

Introduction. Contemporary drug discovery increasingly relies on target-based drug design (TBDD), which enables the rational identification and optimization of bioactive molecules through well-defined molecular targets [1, 2]. Among these targets, cyclooxygenase-2 (COX-2) has attracted considerable attention due to its central role in mediating inflammatory responses and its implication in various pathological conditions, including cancer, pain, and cardiovascular disorders [3, 4]. Selective inhibition of COX-2 remains a pivotal strategy in the development of anti-inflammatory and therapeutic agents with reduced side effects [5, 6].

Molecular docking has emerged as a powerful in silico approach in targeted drug discovery, allowing for the prediction of ligand–protein interactions, evaluation of binding affinities, and prioritization of promising compounds prior to experimental validation [7, 8]. Docking studies are particularly valuable for high-throughput screening of compound libraries, enabling the identification of molecules with favorable interactions within the active site of the target enzyme [9, 10].

Heterocyclic scaffolds, such as thieno[3,2-*d*]pyrimidines, have gained attention in medicinal chemistry owing to their rigid polycyclic framework and versatile chemical reactivity. Several FDA-approved drugs contain the thieno[3,2-*d*]pyrimidine core (Fig. 1), underscoring its suitability as a privileged scaffold for drug design [11].

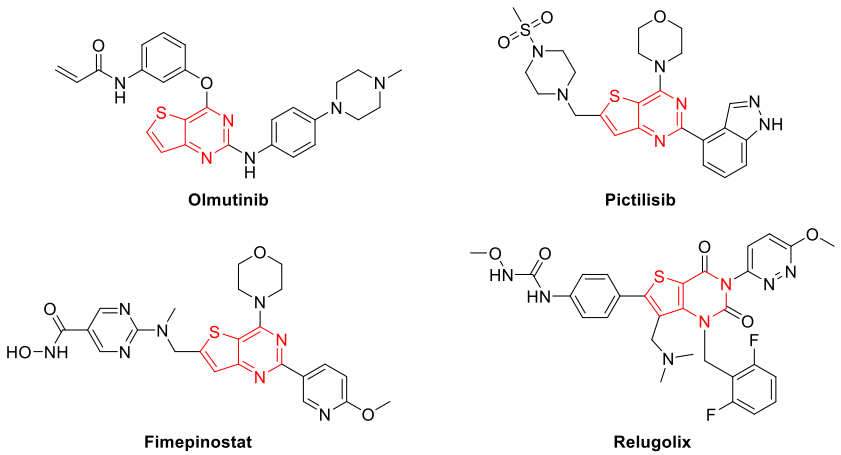
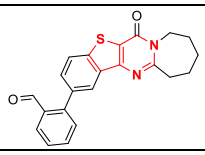
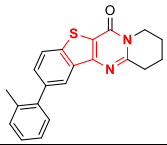
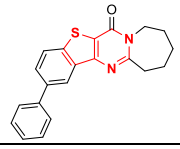
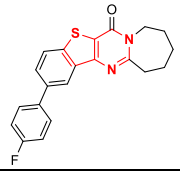
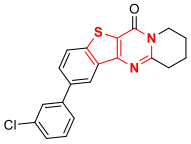
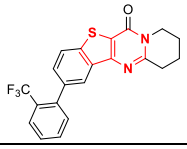
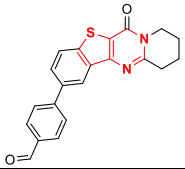
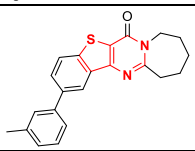
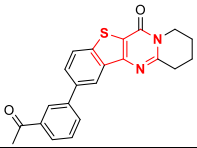


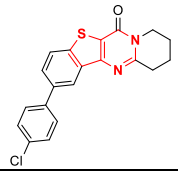
Figure 1. Thieno[3,2-*d*]pyrimidine based drugs used in clinical practice

Tetracyclic thieno[3,2-d]pyrimidine derivatives were selected for this study due to their rigid polycyclic framework, multiple reactive centers, and known potential for biological activity, particularly in modulating enzyme targets. Their structural features provide an ideal scaffold for exploring selective interactions with cyclooxygenase-2 (COX-2). In the present work, a focused library of over 300 thieno[3,2-d]pyrimidine derivatives was virtually screened using molecular docking simulations against the COX-2 active site. The primary objective was to identify promising candidates with strong binding affinity and favorable interactions within the catalytic pocket, which could serve as lead compounds for the development of selective COX-2 inhibitors. The compounds exhibiting the highest docking scores were further analyzed to characterize key hydrogen bonds, π–π stacking, and hydrophobic interactions, providing insights into their potential inhibitory activity and guiding subsequent discussion on their suitability for further optimization.

Research methodology. Molecular docking simulations were performed to evaluate a library of over 300 thieno[3,2-d]pyrimidine derivatives against the cyclooxygenase-2 (COX-2) active site. The crystal structure of COX-2 (PDB ID: 6V3R, resolution 2.66 Å) was obtained from the RCSB Protein Data Bank. Protein and ligand preparations, as well as docking simulations, were carried out using the Schrödinger platform and the OPLS4 force field. The docking protocol was validated by re-docking the co-crystallized ligand and confirming superimposition with the original pose. Molecular docking studies, summarized in Table 1, revealed the binding scores and key interacting residues for the evaluated derivatives and revealed several promising candidates with strong binding affinities. Notably, compounds featuring tetramethylene and pentamethylene rings exhibited the most promising docking scores, suggesting their potential as high-affinity ligands for the COX-2 active site.

Table 1. Binding energies of target compounds

№	Tetracyclic thieno[3,2-*d*]pyrimidines	Binding energy, kcal/mol	Binding residues
1		-11.558	**TYR355, MET522 (aromatic hydrogen bonds) TYR385, TYR387 (π-π stacking interactions) MET113, VAL349, LEU507, ILE517, LEU531 (hydrophobic interactions)**
2		-11.162	**TYR355, MET522 TYR385, TYR387 ARG120 (π-cation interactions) MET113, VAL349, ILE517, MET522**
3		-11.036	**TYR355, MET522 TYR385, TYR387 MET113, LEU507, ILE517, MET522, LEU531**
4		-10.961	**TYR355, MET522 TYR385, TYR387 MET113, VAL349, LEU384, ILE517, MET522, LEU531**
5		-10.907	**TYR355, MET522 TYR385, TYR387 ARG120 MET113, VAL349, LEU359, LEU384, ILE517, MET522, LEU531**
6		-10.848	**TYR355, MET522 TYR385, TYR387 ARG120 MET113, VAL349, ILE517, MET522**
7		-10.766	**TYR355, MET522 TYR385, TYR387 ARG120 MET113, VAL349, LEU359, ILE517, MET522, LEU531**
8		-10.709	**TYR355 TYR385, TYR387 MET113, VAL349, LEU384, LEU507, ILE517, MET522, LEU531**
9		-10.686	**TYR355 TYR387 ARG120 MET113, VAL349, ILE517, MET522, LEU531**

10		-10.614	**TYR355, MET522 TYR385, TYR387 ARG120 MET113, VAL349, LEU384, ILE517, MET522, LEU531**

Among the tested tetracyclic thieno[3,2-*d*]pyrimidine derivatives, compounds **1** and **2** exhibited the highest docking scores, –11.558 kcal/mol and –11.162 kcal/mol, respectively, indicating their strong potential as selective COX-2 inhibitors. Detailed analysis of their binding modes revealed that compound **1** established key aromatic hydrogen bonds with TYR355 (2.49 Å) and MET522 (2.39 Å). π–π stacking interactions were observed with TYR385 and TYR387. Similarly, compound **2** displayed stable aromatic hydrogen bonds with TYR355 (2.46 Å) and MET522 (2.28 Å), π–π stacking interactions with TYR385 and TYR387, and additional π–cation interactions with ARG120. These interactions collectively suggest that both compounds are well accommodated within the COX-2 catalytic pocket and represent promising scaffolds for further optimization (Fig. 2).

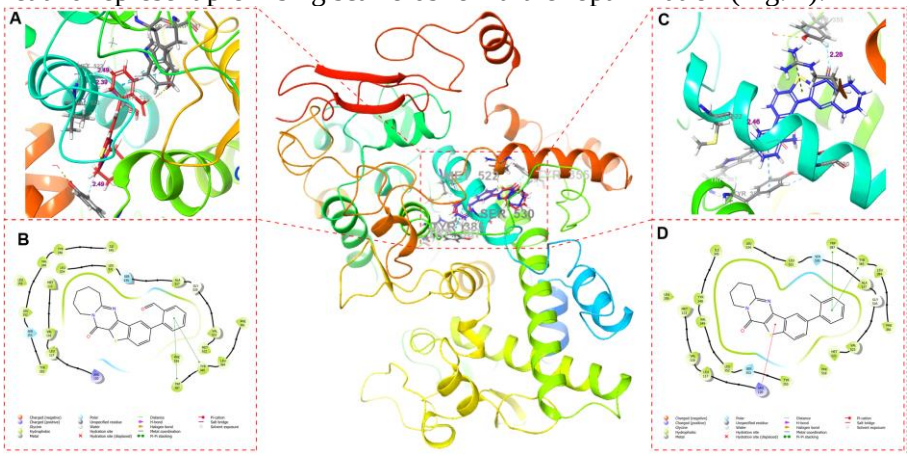


Figure 2. Docking results and 2D interaction diagrams for compounds **1** (A and B) and **2** (C and D)

Compound **1** exhibited hydrophobic interactions with amino acid residues MET113, VAL349, LEU507, ILE517, and LEU531, whereas compound **2** showed similar hydrophobic contacts with MET113, VAL349, ILE517, and MET522 (Fig. 3).

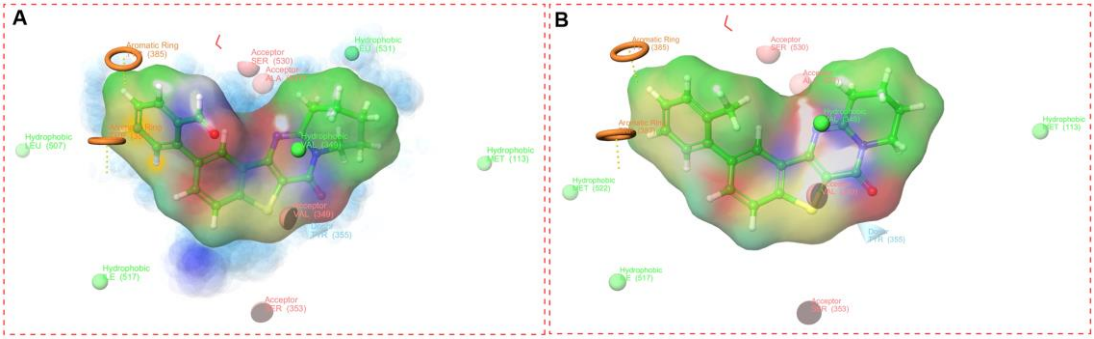


Figure 3. Amino acid residues involved in interactions with compounds **1** (A) and **2** (B)

These results indicate that these tetracyclic thieno[3,2-*d*]pyrimidine derivatives not only fit optimally into the COX-2 catalytic pocket but also engage multiple key interactions essential for inhibitory activity. The high docking scores, combined with favorable binding conformations and extensive active-site contacts, underscore the true potential of these molecules as promising COX-2 inhibitors. Therefore, the functionalized tetracyclic thieno[3,2-*d*]pyrimidine scaffold serves as a robust platform for future structural optimization, providing a reliable foundation for the design of selective and potent cyclooxygenase-2 inhibitors.

Analysis results. Molecular docking studies were performed using the Maestro interface (version 12.8, Schrödinger Suite 2021-2). The X-ray crystal structure of COX-2 (PDB ID: 6V3R, resolution 2.66 Å) was retrieved from the RCSB Protein Data Bank.

Protein preparation was carried out using the Protein Preparation Wizard. Hydrogen atoms were added, bond orders were assigned, and protonation states were adjusted at pH 7.0. Missing side

chains and incomplete residues were modeled using the Prime module. Water molecules located beyond 5 Å from hetero groups were removed.

The chemical structures of the ligands were drawn using ChemOffice Suite 22 and imported into Maestro. Ligand preparation was performed using the LigPrep module. Possible ionization states were generated at pH 7.0 ± 2.0 using Epik, and energy minimization was carried out with the OPLS4 force field under default settings.

The receptor grid was generated by centering the grid box on the co-crystallized ligand, with a grid box size of 12 Å from the centroid. Docking protocol validation was performed by re-docking the co-crystallized ligand into the active site of COX-2. Subsequently, all synthesized compounds were docked into the active site using extra precision (XP) mode.

Conclusion. In conclusion, molecular docking studies provided valuable insights into the binding behavior of the investigated quinazoline derivatives toward the COX-2 active site. Several compounds demonstrated favorable docking scores and stable binding conformations within the catalytic pocket. The observed interactions, including hydrogen bonding, hydrophobic contacts, and π–π stacking interactions, suggest a strong affinity of selected derivatives for the COX-2 enzyme. Notably, compounds exhibiting higher docking scores established key interactions with critical amino acid residues within the active site, indicating their potential as promising COX-2 inhibitors. These findings highlight the quinazoline scaffold as a suitable structural framework for further optimization and structure-based drug design efforts targeting cyclooxygenase-2.

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