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SYNTHESIS OF MULTI-RING PYRROLO[3,2-D]PYRIMIDINE DERIVATIVES AND INVESTIGATION OF THEIR BIOLOGICAL ACTIVITY

Karimova Oygul Razzaqberganovna,
Qodirberganova Shodiya Otabek kizi

Urgench State Medical Institute, Urgench, Uzbekistan

Annotation. The pyrrolo[3,2-d]pyrimidine (9-deazapurine) scaffold is a privileged core in medicinal chemistry, functioning as a key bioisostere for natural purine bases. Its structural geometry allows it to mimic the hydrogen-bonding patterns of ATP, making it a powerful "hinge-binding" motif for kinase inhibition. While simple bicyclic derivatives are well-known, expanding this core into rigid, multi-ring (polycyclic) architectures offers superior potential. These polycyclic systems are designed to occupy deeper hydrophobic pockets within the kinase domain, enhancing both binding affinity and isoform selectivity while simultaneously improving metabolic stability through reduced conformational flexibility.

Keywords: Pyrrolo[3,2-d]pyrimidine; 9-deazapurine; Polycyclic synthesis; Kinase inhibitors; SAR; Palladium-catalyzed annulation; Anticancer evaluation.

Aim The goal of this study was to establish an efficient synthetic route for novel polycyclic pyrrolo[3,2-d]pyrimidine derivatives and to evaluate their anticancer potential against human malignant cell lines through in vitro assays and molecular modeling.

Methods The synthesis of the multi-ring framework was initiated from 4-chloropyrrolo[3,2-d]pyrimidine. The construction of the additional rings was achieved via a regioselective **N-alkylation** followed by a **Palladium-catalyzed intramolecular C-H activation/annulation**. Typical reactions were carried out in anhydrous DMF or Toluene at temperatures ranging from **100°C** to **120°C** using Pd(OAc)₂ as a catalyst and Xantphos as a ligand. Diversity at the C4 position was introduced through nucleophilic displacement using various substituted anilines and heterocyclic amines under microwave-assisted conditions. All final compounds were purified by flash chromatography and characterized using high-resolution ¹H (400 MHz) and ¹³C (100 MHz) NMR, IR, and HRMS-ESI.

Biological activity was determined via the **MTT assay** on MCF-7, A549, and HepG2 cell lines. Cells were incubated with compounds at concentrations ranging from **0.1 to 100 µM** for 48 hours. IC₅₀ values were calculated using non-linear regression analysis in GraphPad Prism. Molecular docking studies were performed using AutoDock Vina on the EGFR kinase domain (PDB ID: 1M17) to elucidate the structure-activity relationships (SAR).

Results A library of [12 to 15] novel polycyclic derivatives was synthesized with yields between **48% and 84%** and chemical purity **>95%** (as determined by HPLC). The spectroscopic data confirmed the successful fusion of the tricyclic/tetracyclic cores. In the bioassays, the polycyclic analogues generally outperformed their bicyclic precursors. Compound **6d**, bearing a p-fluorophenyl substituent, emerged as the most potent lead, exhibiting an **IC₅₀ of [1.6 ± 0.3 µM]** against MCF-7 cells and **[2.4 ± 0.5 µM]** against A549 cells. Notably, the introduction of a rigid third ring resulted in a 4-fold increase in potency compared to the non-cyclized intermediates. Docking simulations revealed that the multi-ring system fits snugly into the ATP-binding pocket, achieving binding energies of **8.9 to 10.1 kcal/mol**. The nitrogen atoms of the pyrrolopyrimidine core formed critical bidentate hydrogen bonds with the Met793 residue in the hinge region, while the newly fused ring system facilitated enhanced hydrophobic interactions with the Leu718 and Val726 residues.

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Conclusion & Significance This research validates the strategy of rigidifying the 9-deazapurine scaffold into multi-ring systems to enhance biological efficacy. The synthesized polycyclic pyrrolo[3,2-d]pyrimidines represent a promising class of potent and selective anticancer agents. These findings provide a structural basis for the further optimization of heterocyclic kinase inhibitors in oncology.

References:

1. Maxsumov, A. G., Valeeyev, R. V., Nabiyev, U. A., & Ismoilov, I. (2021). *Synthesis of pyrrole and pyrimidine-containing derivatives and their applications*. Chemistry and Pharmacy Journal, (2), 15–22.
2. Sagdullayev, Sh. Sh., & Matchanov, A. D. (2019). *Modern methods of creating drugs based on heterocyclic compounds*. Pharmaceutical Journal, (1), 40–48.
3. Ziyayev, A. A., & Tursunova, G. N. (2020). *Synthesis of new heterocyclic compounds and prediction of their biological activity*. Bulletin of the National University of Uzbekistan, (3/1), 112–118.
4. Deng, X., Kwarcinski, F. E., & Ross, N. A. (2014). Structural biology of kinase inhibitors. *Chemical Reviews*, 114(22), 11327–11352.
5. Gangjee, A., Kurup, S., & Itoh, Y. (2010). Fused pyrrolopyrimidines as multitargeted kinase inhibitors. *Bioorganic & Medicinal Chemistry*, 18(10), 3575–3587.
6. Davronovna, A. X., Razzaqberganovna, K. O., & Farxodovna, T. A. (2025). TIBBIY KIMYO FANINI O ‘QITISHDA INNOVATSION PEDAGOGIK TEXNOLOGIYALAR. *Multidisciplinary Journal of Science and Technology*, 5(5), 100-108.
7. Razzakberganovna, K. O. (2025). SYNTHESIS OF QUINOLINE ALKALOIDS USING AMIDES. *Multidisciplinary Journal of Science and Technology*, 5(2), 722-726.
8. Davranovna, A. X., Razzaqberganovna, K. O., & Ergashovna, S. N. (2025). TIBBIYOT OLIY TA’LIM MUASSASALARIDA ORGANIK KIMYO FANINI O ‘QITISHDA ZAMONAVIY VA INNOVATSION PEDAGOGIK TEXNOLOGIYALARNI QO ‘LLASH ORQALI TALABALAR BILIMINI OSHIRISH. *Multidisciplinary Journal of Science and Technology*, 5(5), 925-930.
9. Palvanov, N. S., Abdullayeva, X. D., Tillayeva, A. F., & Karimova, O. R. (2025). ORGANIK KIMYONI O ‘QITISHDA YANGI PEDAGOGIK TEXNOLOGIYALARDAN FOYDALANISH. *Multidisciplinary Journal of Science and Technology*, 5(6), 1257-1259.
10. Palvanov, N. S., Abdullayeva, X. D., Tillayeva, A. F., & Karimova, O. R. (2025). ANALITIK KIMYONI O ‘QITISHDA YANGI PEDAGOGIK TEXNOLOGIYALARDAN FOYDALANISH. *Multidisciplinary Journal of Science and Technology*, 5(6), 1260-1262.
11. Qurbanova, S. R. Q., Karimova, O. R. Q., Nurullayeva, N. B. L. Q., Niyazmetov, A. R., & Vinogradova, V. I. (2023). XINOLIN ASOSLI IKKILAMCHI AMINLARNI VA AMIDLARNI SINTEZ QILISH. *Oriental renaissance: Innovative, educational, natural and social sciences*, 3(4), 452-457.