# SYNTHESIS OF *N*-(4-(((6-NITROQUINAZOLIN-4-YL)AMINO)METHYL)PHENYL)MORPHOLINE-4-CARBOXAMIDE

**Gaybullaev Shukhrat**
Assistant at Samarkand State University named after Sharof Rashidov
Email: shukhratbekgaybullayev@gmail.com
https://orcid.org/0009-0003-7753-4262
**Takhirov Yuldash**
Associate Professor at Urgench State University named after Abu Rayhan Biruni
Email: yuldash_78@mail.ru
https://orcid.org/0000-0001-5281-9446
**Zohidov Kosim**
Associate Professor at Samarkand State University named after Sharof Rashidov
Email: z-qosim@samdu.uz
https://orcid.org/0009-0009-3658-3256
**Bozorov Khurshed**
Professor at Samarkand State University named after Sharof Rashidov
Email: khurshedbek@gmail.com
https://orcid.org/0000-0001-7449-0936

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**Abstract**: Quinazolines, as fused bicyclic heterocycles, are of particular importance in organic synthesis and medicinal chemistry. In the present study, the targeted synthesis of a novel compound, *N*-(4-(((6-nitroquinazolin-4-yl)amino)methyl)phenyl)morpholine-4-carboxamide, was achieved in high yield. This molecule represents a key intermediate for the preparation of 4,6-disubstituted quinazoline derivatives. The structure of the obtained compound was confirmed by modern physicochemical methods, including $^{1}$H NMR, $^{13}$C NMR, and HRMS.

**Keywords**: quinazoline, organic synthesis, cyclization, substitution reactions, chlorination, targeted synthesis

**Annotatsiya**: Xinazolinlar tutash bisiklik geterosiklik tizim sifatida organik sintez va tibbiy kimyoda alohida ahamiyat kasb etadi. Mazkur tadqiqotda 4,6-dialmashgan xinazolin hosilalarini olish uchun muhim oraliq modda hisoblangan yangi *N*-(4-(((6-nitroxinazolin-4-il)amino)metil)fenil)morfolin-4-karboksamid birikmasining maqsadli sintezi yuqori unum bilan amalga oshirildi. Olingan birikmaning tuzilishi zamonaviy fizik-kimyoviy tahlil usullari, jumladan $^{1}$H YaMR, $^{13}$C YaMR va HRMS yordamida tasdiqlandi.

**Kalit so‘zlar**: xinazolin, organik sintez, halqalanish, almashinish reaksiyalari, xlorlash, maqsadli sintez

**Аннотация**: Хиназолины, являясь конденсированными бициклическими гетероциклами, имеют особое значение в органическом синтезе и медицинской химии. В настоящей работе осуществлён целенаправленный синтез нового соединения *N*-(4-(((6-нитрохиназолин-4-ил)амино)метил)фенил)морфолин-4-карбоксамида, представляющего собой важный промежуточный продукт для получения 4,6-дизамещённых производных хиназолина. Структура полученного соединения подтверждена современными физико-химическими методами анализа, включая $^{1}$H ЯМР, $^{13}$C ЯМР и HRMS.

**Ключевые слова**: хиназолин, органический синтез, циклизация, реакции замещения, хлорирование, направленный синтез.

## Introduction

Nitrogen-containing heterocycles occupy a central position in medicinal chemistry due to their broad spectrum of pharmacological activities and synthetic versatility. Among them, the quinazoline scaffold has emerged as a privileged structure frequently employed in the design of biologically active molecules [1, 2]. Numerous quinazoline derivatives have demonstrated diverse therapeutic properties, including antimicrobial, anti-inflammatory, anticonvulsant, antihypertensive, antiviral, and particularly anticancer activities [3].

Quinazoline-based compounds have attracted considerable attention as inhibitors of protein kinases, which play critical roles in cell proliferation, differentiation, and survival. Dysregulation of kinase signaling pathways is closely associated with tumor initiation and progression, making them important targets for anticancer drug discovery. In recent years, 4-aminoquinazoline derivatives have been extensively investigated because of their strong inhibitory potency toward various tyrosine and serine/threonine kinases [4, 5].

The clinical relevance of this scaffold is highlighted by several quinazoline-containing drugs approved by the U.S. Food and Drug Administration (FDA), such as Afatinib, Lapatinib, Vandetanib, and Tucatinib (Figure 1). Despite these advances, the emergence of resistance, limited selectivity, and adverse effects continue to drive the search for novel quinazoline derivatives with improved pharmacological profiles [6, 7].

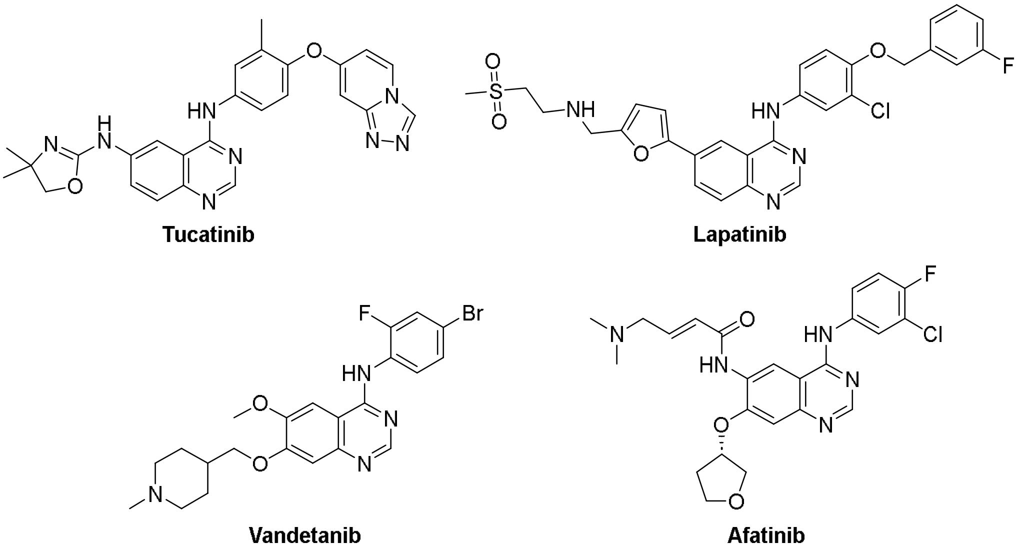


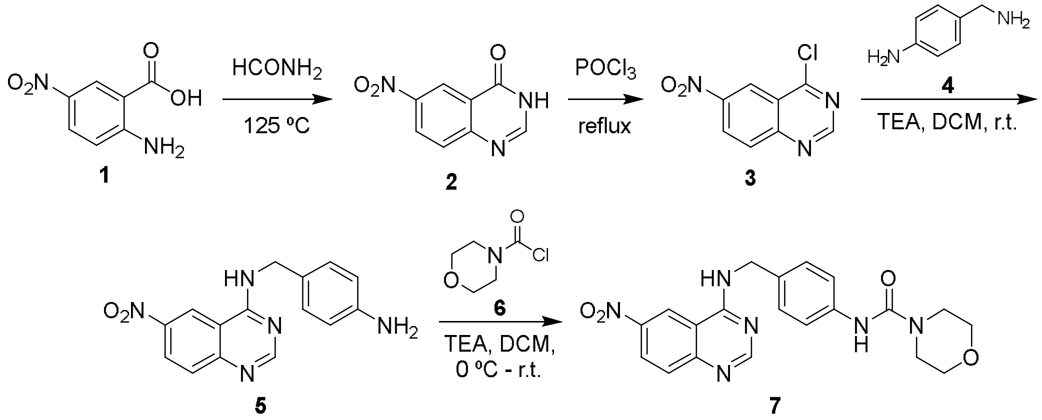
**Figure 1.** FDA approved 4-aminoquinazoline drugs in the market

Structurally, quinazoline offers multiple substitution sites and the ability to form key hydrophobic interactions and hydrogen bonds within enzyme active pockets [8]. These features, combined with the availability of diverse synthetic methodologies, make it an attractive template for rational drug design. Based on these considerations, the present study is directed toward the development of an efficient synthetic route to a valuable quinazoline-based precursor. The obtained intermediate is expected to serve as a versatile platform for further structural modification and the preparation of diverse 4,6-disubstituted quinazoline derivatives for future medicinal chemistry investigations.

## Research methodology

The quinazoline nucleus possesses several reactive centers that enable broad opportunities for chemical functionalization and make it an attractive platform for the preparation of structurally diverse derivatives. In particular, 4,6-disubstituted quinazolines continue to draw attention because suitably designed intermediates within this class allow straightforward access to libraries of compounds for subsequent biological investigations. Therefore, the development of practical and reliable routes to key precursors remains an essential task in synthetic medicinal chemistry. In the present work, we established an efficient synthetic pathway toward a functionalized 4-amino-6-nitroquinazoline derivative. The strategy relied on the preparation of a chloro-activated intermediate followed by nucleophilic substitution and final acylation, enabling the rapid assembly of a suitably elaborated synthon.

The synthesis commenced from commercially available 5-nitroanthranilic acid (**1**). In the first step, compound **1** underwent Niementowski cyclization with formamide under solvent-free conditions at 125 °C, affording 6-nitroquinazolin-4(3*H*)-one (**2**). In the subsequent step, chlorination of compound **2** with $POCl_3$, also under solvent-free conditions, provided 4-chloro-6-nitroquinazoline (**3**). The activated chloride **3** was then subjected to selective nucleophilic substitution with 4-aminobenzylamine (**4**) in dichloromethane (DCM) in the presence of triethylamine (TEA) at room temperature, furnishing intermediate **5**. Finally, the free amino group of intermediate 5 was acylated by the gradual addition of morpholinecarbonyl chloride (**6**) in DCM at 0 °C under basic conditions. This transformation proceeded smoothly and delivered the desired nitro compound, *N*-(4-(((6-nitroquinazolin-4-yl)amino)methyl)phenyl)morpholinecarboxamide (**7**), in good yield (Scheme 1):



**Scheme 1.** Synthesis of key precursor *N*-(4-(((6-nitroquinazolin-4-yl)amino)methyl)phenyl)morpholinecarboxamide (**7**)

## Analysis results

The starting materials were obtained from commercial suppliers and used without further purification. All solvents, including ethanol, petroleum ether, toluene, ethyl acetate, and 1,2-dichloroethane, were anhydrous to avoid moisture interference. Reaction progress was monitored by thin-layer chromatography (TLC) on $HSGF_{254}$ silica plates (2.5 × 5 cm), with samples applied using 0.3 × 100 mm glass microcapillaries. Chromatograms were visualized under UV light at 254 and 365 nm or by iodine staining. Tetramethylsilane (TMS) was used as an internal standard in NMR analysis. Structural characterization was carried out using $^{1}$H and $^{13}$C NMR spectra recorded on a VARIAN 400 MHz spectrometer at room temperature. HRMS was performed on a QTRAP® 6500+ LC-MS system to confirm molecular composition and structure.

**6-Nitroquinazolin-4(3*H*)-one (2)**. Yield 85%, light brown solid, Mp 133–134 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.78 (d, $J$ = 2.7 Hz, 1H), 8.53 (dd, $J$ = 9.0, 2.7 Hz, 1H), 8.32 (s, 1H), 7.85 (d, $J$ = 9.0 Hz, 1H).

**4-Chloro-6-nitroquinazoline (3).** Yield 73%, light yellow solid, Mp 140–142 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.81 (d, $J$ = 2.7 Hz, 1H), 8.56 (dd, $J$ = 8.9, 2.7 Hz, 1H), 8.36 (s, 1H), 7.88 (d, $J$ = 9.0 Hz, 1H).

***N*-(4-aminobenzyl)-6-nitroquinazolin-4-amine (5).** Yield 91%, light yellow solid, Mp 145–146 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.42 (d, $J$ = 2.5 Hz, 1H), 9.38 (t, $J$ = 5.8 Hz, 1H), 8.59 (s, 1H), 8.46 (dd, $J$ = 9.2, 2.5 Hz, 1H), 7.81 (d, $J$ = 9.2 Hz, 1H), 7.06 (d, $J$ = 8.3 Hz, 2H), 6.52 (d, $J$ = 8.3 Hz, 2H), 5.01 (s, 2H), 4.62 (d, $J$ = 5.6 Hz, 2H).

***N*-(4-(((6-nitroquinazolin-4-yl)amino)methyl)phenyl)morpholine-4-carboxamide** (**7**). Yield 88%, yellow solid, Mp 140–142 °C. $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.54 (t, $J$ = 5.7 Hz, 1H 1H), 9.45 (d, $J$ = 2.5 Hz, 1H), 8.60 (s, 1H), 8.57 (s, 1H), 8.48 (dd, $J$ = 9.2, 2.4 Hz, 1H), 7.84 (d, $J$ = 9.2 Hz, 1H), 7.42 (d, $J$ = 8.5 Hz, 2H), 7.26 (d, $J$ = 8.4 Hz, 2H), 4.73 (d, $J$ = 5.7 Hz, 2H), 3.62 – 3.56 (m, 4H), 3.43 – 3.38 (m, 4H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 160.58, 158.73, 155.61, 153.36, 153.32, 144.48, 139.80, 132.27, 129.49, 129.16, 128.11, 126.75, 126.68, 121.11, 120.09, 114.52, 114.13, 66.42, 44.56, 44.02. HRMS (ESI) calcd for $C_{22}H_{23}N_5O_3$ [M+H]+ 409.1624 found 409.1632.

## Conclusion

In conclusion, the nitro-containing quinazoline derivative *N*-(4-(((6-nitroquinazolin-4-yl)amino)methyl)phenyl)morpholinecarboxamide (**7**) was successfully prepared through a practical and efficient multistep synthetic sequence. The developed route, involving cyclization, chlorination, regioselective nucleophilic substitution, and final acylation, proved to be reliable and reproducible, providing the desired product in good yield and high purity. The structures of all synthesized intermediates and the final compound were unambiguously confirmed by $^{1}$H NMR, $^{13}$C NMR, and HRMS analyses. Importantly, the obtained nitroquinazoline (**7**) represents a valuable and functionally rich precursor, offering broad opportunities for subsequent transformations and diversification of the quinazoline framework. Thus, the presented methodology establishes a convenient platform for the future preparation of structurally diverse derivatives and supports ongoing efforts toward the discovery of new biologically active quinazoline-based molecules.

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## References

1. Marshall, C.M., et al., An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013-2023). J Med Chem, 2024. 67(14): p. 11622-11655.
2. Vitaku, E., D.T. Smith, and J.T. Njardarson, Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J Med Chem, 2014. 57(24): p. 10257-74.
3. Bala, I.A., A.M. Asiri, and R.M. El-Shishtawy, Quinazoline derivatives and hybrids: recent structures with potent bioactivity. Medicinal Chemistry Research, 2024. 33(12): p. 2372-2419.
4. Das, D. and J. Hong, Recent advancements of 4-aminoquinazoline derivatives as kinase inhibitors and their applications in medicinal chemistry. Eur J Med Chem, 2019. 170: p. 55-72.
5. Herrera-Vázquez, F.S., F. Hernández-Luis, and J.L. Medina Franco, Quinazolines as inhibitors of chromatin-associated proteins in histones. Medicinal Chemistry Research, 2019. 28(4): p. 395-416.
6. Haghighijoo, Z., et al., Therapeutic potential of quinazoline derivatives for Alzheimer's disease: A comprehensive review. Eur J Med Chem, 2022. 227: p. 113949.
7. Shagufta and I. Ahmad, An insight into the therapeutic potential of quinazoline derivatives as anticancer agents. Medchemcomm, 2017. 8(5): p. 871-885.
8. Ayala-Aguilera, C.C., et al., Small Molecule Kinase Inhibitor Drugs (1995-2021): Medical Indication, Pharmacology, and Synthesis. J Med Chem, 2022. 65(2): p. 1047-1131.