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SYNTHESIS OF N-(4-(((7-NITROQUINAZOLIN-4-YL)AMINO)METHYL)PHENYL)CYCLOHEXANECARBOXAMIDE

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Abstract. Quinazoline derivatives are important heterocyclic compounds with significant roles in organic synthesis and drug design, with 4-aminoquinazoline derivatives being particularly noteworthy due to their biological activity. In this study, the key precursor *N*-(4-(((7-nitroquinazolin-4-yl) amino) methyl) phenyl)cyclohexanecarboxamide was successfully synthesized in high yield and with operational simplicity. The structure and purity of the synthesized compound were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS, highlighting its potential as a versatile scaffold for further medicinal and biological investigations.

Keywords: drug design, quinazoline derivatives, acylation, nucleophilic substitution, condensation, chlorination.

N-(4-(((7-Nitroxinazolin-4-il)amino) metil) fenil) siklogeksankarboksamid sintezi

Annotatsiya. Xinazolin hosilalari organik sintez va dori vositalari dizaynida muhim ahamiyatga ega bo‘lgan geterosiklik birikmalar bo‘lib, ayniqsa 4-aminoxinazolin hosilalari biologik jihatdan faol modda sifatida alohida e’tiborga loyiqdir. Ushbu tadqiqotda, maqsadli sintezlar uchun kalit prekursor hisoblangan *N*-(4-(((7-nitroxinazolin-4-il)amino) metil) fenil) siklogeksankarboksamid yuqori hosildorlik va qayta ishlab chiqarish qulayligi bilan muvaffaqiyatli sintez qilindi. Olingan birikmaning struktura va tozaligi ^{1}H YaMR, ^{13}C YaMR va HRMS kabi fizik-kimyoviy usullar yordamida tasdiqlandi, bu esa uni kelajakdagi biologik va farmatsevtik tadqiqotlar uchun muhim sinton sifatida ajratib turadi.

Kalit so‘zlar: dori vositalari dizayni, xinazolin hosilalari, atsillash, nukleofil almashinish, kondensatsiya, xlorlash.

Синтез *N*-(4-(((7-нитрохиназолин-4-ил)амино)метил)фенил)циклогексанкарбоксамида

Аннотация. Производные хиназолина являются важными гетероциклическими соединениями, играющими значительную роль в органическом синтезе и дизайне лекарственных средств, при этом производные 4-аминохиназолина особенно ценны благодаря своей биологической активности. В данном исследовании ключевой прекурсор *N*-(4-(((7-нитрохиназолин-4-ил)амино)метил)фенил)циклогексанкарбоксамид был успешно синтезирован с высокой выходностью и удобством

проведения реакции. Структура и чистота синтезированного соединения были подтверждены методами ^{1}H ЯМР, ^{13}C ЯМР и HRMS, что подчеркивает его потенциал в качестве универсального скелета для дальнейших медицинских и биологических исследований.

Ключевые слова: дизайн лекарственных средств, производные хиназолина, ацилирование, нуклеофильное замещение, конденсация, хлорирование.

Introduction. Contemporary drug discovery faces several inherent challenges, including high attrition rates, long development timelines, and escalating costs. In this context, target-based drug design (TBDD) has emerged as a powerful and efficient strategy, enabling the rational identification, optimization, and prioritization of bioactive molecules by focusing on specific molecular targets [1]. TBDD facilitates a more systematic and predictable approach to drug discovery, reducing the likelihood of late-stage failures and increasing the efficiency of identifying promising candidates for further development. Notably, the proportion of newly approved drugs developed through TBDD strategies has steadily increased in recent years [2].

Among small-molecule therapeutics, kinase inhibitors represent a major class, largely due to advances in computational modeling, structure-based design, and molecular docking techniques [3, 4]. Many of these inhibitors are derived from heterocyclic scaffolds, which are privileged structures in medicinal chemistry. In particular, quinazoline-based derivatives, considered bioisosteric analogues of purines, have attracted considerable attention owing to their strong affinity for ATP-binding sites of kinases and their proven clinical relevance [5-7]. The quinazoline ring is a fused heterocyclic system composed of a pyrimidine and a benzene ring, which provides multiple reactive centers for chemical modification. Owing to these unique properties, quinazoline derivatives are widely utilized in the design of kinase inhibitors and other bioactive molecules [8, 9]. Consequently, several quinazoline-based derivatives with inhibitory activity against diverse molecular targets have been approved by the FDA, highlighting their importance in modern drug discovery and development [10-12] (Figure 1):

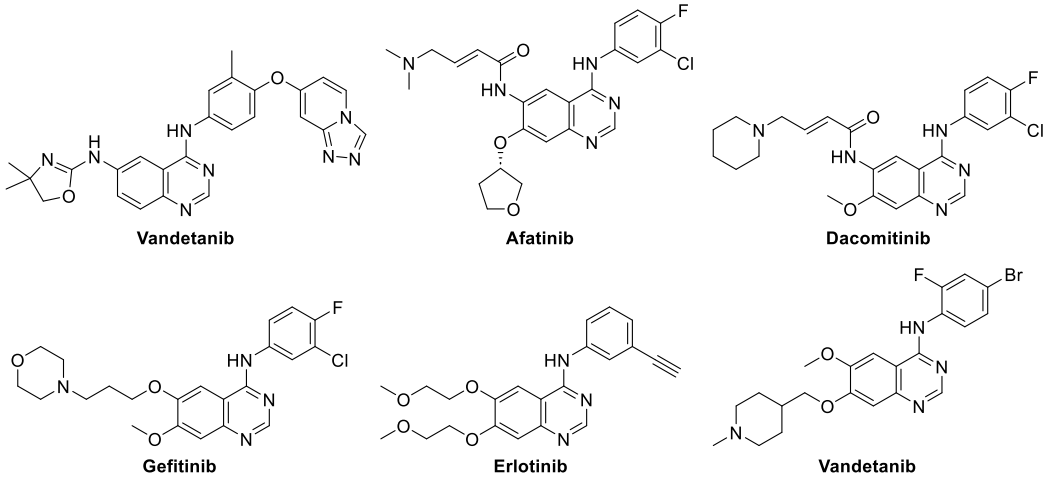
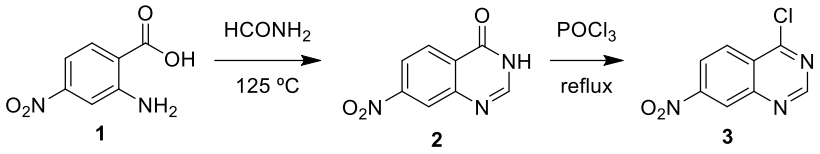


Figure 1. Quinazoline based drugs used in clinical practice

The quinazoline scaffold possesses multiple reactive centers, making it a highly versatile platform for chemical modification and drug design. In particular, 4,7-disubstituted quinazoline derivatives have attracted significant attention due to their recognized biological activity, and the development of new, efficient precursors for this class remains a valuable objective. In this study, we focused on the synthesis of a 4-amino-7-nitroquinazoline derivative as a key intermediate, which can serve as a versatile scaffold for subsequent structural modifications. Using a straightforward and efficient synthetic route, 4-chloro-7-nitroquinazoline was first obtained and then converted into the key precursor *N*-(4-(((7-nitroquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide in good

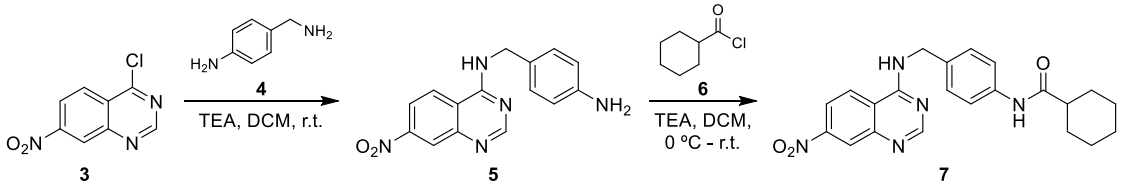
yield. This intermediate provides a practical foundation for the design and development of novel 4,7-disubstituted quinazoline derivatives with potential biological activity.

Research methodology. The synthesis commenced from commercially available 4-nitroanthranilic acid (**1**), which was selected as a readily accessible and structurally suitable starting material for the construction of the quinazoline core. In the first step, compound **1** underwent intramolecular cyclization with formamide via a classical Niementowski reaction under solvent-free conditions at 125 °C, leading to the formation of 7-nitroquinazolin-4(3*H*)-one (**2**) in good yield. This transformation efficiently established the quinazolinone scaffold, which is a key pharmacophoric motif in numerous kinase inhibitors. In the subsequent step, compound 2 was subjected to chlorination using phosphorus oxychloride ($POCl_3$) under solvent-free conditions. This reaction resulted in the selective conversion of the 4-oxo group into the corresponding 4-chloro functionality, affording 4-chloro-7-nitroquinazoline (**3**). The introduction of the chloro substituent at the C-4 position generated an activated electrophilic center, rendering compound **3** a versatile intermediate for further nucleophilic substitution reactions in the downstream synthesis of target derivatives (Scheme 1):



Scheme 1. Synthesis of 4-chloro-7-nitroquinazoline (**3**)

Subsequently, the activated intermediate 4-chloro-7-nitroquinazoline (**3**) was subjected to a selective nucleophilic aromatic substitution reaction with 4-aminobenzylamine (**4**). The reaction was carried out under mild basic conditions using triethylamine (TEA) as a base in dichloromethane (DCM) at room temperature. Under these conditions, the chlorine atom at the C-4 position was efficiently displaced by the amino group, affording *N*-(4-aminobenzyl)-7-nitroquinazolin-4-amine (**5**) in satisfactory yield. This step successfully introduced a flexible linker containing a terminal amino group, providing a suitable handle for further functionalization. In the final step of the synthetic sequence, intermediate **5** was further derivatized through an acylation reaction. The free amino group was reacted with cyclohexanecarbonyl chloride (**6**), which was added dropwise at 0 °C in an ice bath under basic conditions (TEA) in DCM. The reaction mixture was then allowed to warm to room temperature and stirred to completion, resulting in the formation of the key precursor *N*-(4-(((7-nitroquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide (**7**) (Scheme 2):



Scheme 2. Synthesis of key precursor *N*-(4-(((7-nitroquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide (**7**)

Overall, the successful synthesis of compound 7 established it as a key nitro-functionalized quinazoline precursor for further chemical elaboration. Importantly, the presence of the nitro group provides a versatile synthetic handle, enabling subsequent reduction and functional group transformations in later stages of the study.

At the present stage, compound 7 was isolated and fully characterized as a stable and synthetically accessible intermediate. Although the reduction of the nitro group was not carried out at this stage, this functionality is intended for future conversion into the corresponding amino group, which will allow the introduction of diverse substituents through amide formation and related transformations. Such modifications are expected to facilitate the generation of structurally diverse quinazoline derivatives and enable systematic investigation of their structure–activity relationships (SAR).

Therefore, compound **7** represents a crucial precursor in the overall synthetic strategy, serving as a foundation for future derivatization and the development of biologically active quinazoline-based inhibitors.

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.

7-Nitroquinazolin-4(3*H*)-one (2). Compound **1** (0.182 g, 1.0 mmol) was heated with formamide (5 mL) under reflux with continuous stirring for 5 h. The reaction progress was monitored by TLC. After completion, the reaction mixture was cooled to room temperature, resulting in the formation of a precipitate. The solid product was collected by vacuum filtration, washed with distilled water, and dried under reduced pressure to afford compound **2**. Yield 82%, light brown solid, Mp 127–129 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.34 (d, J = 2.2 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.25 (s, 1H), 8.22 (dd, J = 8.7, 2.3 Hz, 1H).

4-Chloro-7-nitroquinazoline (3). Compound **2** (0.191 g, 1.0 mmol) was added to phosphorus oxychloride ($POCl_3$, 5 mL) and the mixture was refluxed with stirring for 6 h. Reaction progress was monitored by TLC. After completion, the reaction mixture was cooled and slowly poured onto crushed ice–water with vigorous stirring. The resulting precipitate was collected by vacuum filtration, washed thoroughly with cold water, and dried under reduced pressure to afford compound **3**. Yield 71%, light yellow solid, Mp 137–139 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 2.2 Hz, 1H), 8.34 (d, J = 8.7 Hz, 1H), 8.31 (s, 1H), 8.24 (dd, J = 8.7, 2.3 Hz, 1H).

***N*-(4-Aminobenzyl)-7-nitroquinazolin-4-amine (5).** Compound **3** (0.209 g, 1.0 mmol) and 4-(aminomethyl)aniline (**4**) (0.146 g, 1.2 mmol) were dissolved in DCM (5 mL), followed by the addition of triethylamine (0.202 g, 2.0 mmol). The reaction mixture was stirred at room temperature overnight, and the progress was monitored by TLC. After completion, the mixture was diluted with water and extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using DCM/MeOH as the eluent to afford intermediate **5**. Yield 90%, yellow solid, Mp 150–151 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (t, J = 5.9 Hz, 1H), 8.60 (s, 1H), 8.56 (d, J = 9.1 Hz, 1H), 8.40 (d, J = 2.4 Hz, 1H), 8.24 (dd, J = 9.0, 2.4 Hz, 1H), 7.06 (d, J = 8.3 Hz, 2H), 6.52 (d, J = 8.3 Hz, 2H), 5.07 (s, 2H), 4.63 (d, J = 5.8 Hz, 2H).

***N*-(4-(((7-Nitroquinazolin-4-yl)amino)methyl)phenyl)cyclohexanecarboxamide (7).** Intermediate **5** (0.295 g, 1.0 mmol) was dissolved in dichloromethane (5 mL) and the solution was cooled to 0 °C. Triethylamine (0.303 g, 3.0 mmol) was added, followed by the dropwise addition of cyclohexanecarbonyl chloride (**6**) (0.294 g, 2.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. Reaction progress was monitored by TLC. Upon completion, the mixture was worked up with water and extracted with dichloromethane. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (DCM/MeOH) to afford compound **7**. Yield 70%, light yellow solid, Mp 140–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.22 (t, J = 5.7 Hz, 1H), 8.60 – 8.53 (m, 2H), 8.41 (d, J = 2.4 Hz, 1H), 8.26 (dd, J = 9.0, 2.4 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 4.74 (d, J = 5.6 Hz, 2H), 2.35 – 2.23 (m, 1H), 1.85 – 1.58 (m, 5H), 1.44 – 1.13 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.18, 159.08, 159.00, 157.02, 149.90, 149.20, 138.41, 133.02, 127.71, 125.35, 122.66, 119.05, 118.55, 44.79, 43.50, 29.13, 25.39, 25.23.

Conclusion. The *N*-(4-(((7-nitroquinazolin- 4-yl) amino) methyl) phenyl) cyclohexanecarboxamide (**7**) intermediate was efficiently synthesized through a concise, high-yielding

method. The sequence, involving Niementowski cyclization, targeted nucleophilic substitution, and controlled acylation, afforded the compound with excellent purity. Comprehensive characterization by ^{1}H and ^{13}C NMR, along with HRMS, confirmed the structural integrity of both intermediates and the final product. As a strategically important key precursor, compound (**7**) provides a versatile framework for the construction of a variety of quinazoline derivatives. This scaffold holds promise for the rational design of novel bioactive molecules and further investigation in medicinal chemistry programs targeting therapeutically relevant quinazoline-based agents.

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