JCRS Journal of Chemical Reactivity and Synthesis 2024: 14(4) 315-331

Research Article

Synthesis and Structural Characterization of Novel Quinazoline–Thiadiazole–Aryl-Urea Derivatives with Ortho-Substituted Aryl Groups

Sara Masoudinia[a], Marjaneh Samadizadeh[a], Alireza Foroumadi[b,c], Hamidreza Bijanzadeh[d]

Maliheh Safavi[e]

[a] Department of Chemistry, CT.C., Islamic Azad University, Tehran, Iran

[b] Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

[c] Drug Design and Development Research Center, The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran

[d] Department of Environment, Faculty of Natural Resources and Marine Sciences, TarbiatModares University, Tehran, Iran

[e] Department of Biotechnology, Iranian Research Organization for Science and Technology (IROST), Tehran, Iran

ARTICLEINFO

Received:
22 August 2025

Accepted:
18 September 2025

Available online:
22 September 2025

✉: M. Samadizadeh
dr.samadizadeh@iau.ac.ir

ABSTRACT:

Quinazoline and 1,3,4-thiadiazole scaffolds represent privileged heterocycles with broad pharmacological relevance, particularly in the design of anticancer drug candidates. In this study, a novel series of four quinazoline–thiadiazole aryl-urea derivatives (9a–d) was synthesized via a concise two-step protocol. The synthetic route comprised (i) initial coupling of 5-amino-1,3,4-thiadiazole-2-thiol with aryl isocyanates to afford N-aryl urea intermediates (8a–d), followed by (ii) nucleophilic aromatic substitution (SNAr) of the thiadiazole moiety with 4-chloro-6-nitroquinazoline to yield the final products (9a–d). The target compounds were obtained in moderate to good yields (62–78%) as crystalline solids. Structural elucidation was achieved using IR, ^{1}H and ^{13}C NMR spectroscopy, ESI-MS, melting point determination, and elemental analysis, which collectively confirmed the proposed structures. The design strategy was informed by previous work on structurally related quinazoline–thiadiazoleureas with MTT-validated antiproliferative activity, underscoring these new derivatives as promising candidates for subsequent biological evaluation.

Keywords: quinazoline; 1, 3, 4-thiadiazole; aryl urea; synthesis; structural characterization;Anticancer-oriented design

1. Introduction

Heterocyclic compounds have long been recognized as fundamental scaffolds in medicinal chemistry owing to their remarkable structural diversity and capacity to engage a wide range of biological targets[1-4].

The inclusion of heterocycles into drug molecules frequently enhances binding affinity, target selectivity, and pharmacokinetic profiles, contributing to their widespread presence among FDA-approved therapeutics for various diseases, including cancer, infectious diseases, and neurological disorders [5-10] . Recent analyses indicate that over 75% of small-molecule drugs contain at least one heterocyclic ring, highlighting the critical role of these motifs in modern drug design[3, 11, 12]. Consequently, the rational design and continuous exploration of novel heterocyclic frameworks remain a central strategy for identifying bioactive molecules with improved efficacy and reduced toxicity[13-15]. Moreover, strategic modification of heterocyclic cores enables fine-tuning of lipophilicity, solubility, and metabolic stability, further optimizing their pharmacological performance, and clinical potential.

Quinazolines and quinazolinones have emerged as privileged heterocyclic scaffolds in anticancer drug discovery due to their ability to modulate key signaling pathways. Clinically approved drugs, such as Gefitinib and Erlotinib, incorporate quinazoline cores that selectively inhibit epidermal growth factor receptor (EGFR) tyrosine kinases, resulting in significant antiproliferative effects against a range of solid tumors[16-20]. Extensive medicinal chemistry efforts have focused on structural modifications of the quinazoline nucleus to enhance target specificity, circumvent acquired resistance, and optimize pharmacokinetic and pharmacodynamic properties [10, 21-25] .

Fused quinazoline systems, including benzo[g]quinazolinones, introduce increased planarity and aromaticity, facilitating efficient DNA intercalation and enzyme binding interactions, which can further potentiate cytotoxic activity[26-30]. Additionally, substitution patterns on the heterocyclic ring have been correlated with improved metabolic stability and reduced off-target effects, making these scaffolds highly versatile for the development of novel anticancer agents.

1, 3, 4-Thiadiazole derivatives represent a versatile class of heterocycles that have attracted considerable attention in medicinal chemistry due to their wide spectrum of biological activities, including anticancer, antibacterial, antifungal, and anti-inflammatory effects[31-

36]. The presence of both sulfur and nitrogen atoms in the five-membered ring imparts distinct electronic characteristics and the ability to form multiple hydrogen bonds, which can enhance ligand–target interactions and improve binding affinity towards enzymes and receptors [9, 37-40] . Several thiadiazole-containing compounds have demonstrated potent cytotoxicity against cancer cell lines, with IC50 values in the low micromolar range, highlighting their potential as lead structures[41-43]. Moreover, the integration of thiadiazole motifs into hybrid molecules has proven an effective strategy to generate multifunctional bioactive agents, combining diverse pharmacophores within a single scaffold [44, 45].
These properties make thiadiazole derivatives promising candidates for the rational design of next-generation therapeutic agents with optimized efficacy and selectivity.

Urea moieties are widely utilized in medicinal chemistry owing to their ability to act simultaneously as hydrogen bond donors and acceptors, thereby enhancing molecular recognition and target engagement[46-50]. The conformational flexibility of the urea group enables it to establish stable hydrogen-bonding networks with amino acid residues in protein active sites, often improving binding affinity and residence time. Importantly, urea derivatives have been extensively reported as kinase inhibitors, with several clinically relevant drugs such as Sorafenib and Regorafenib exploiting this functional group to modulate aberrant signaling pathways implicated in cancer and inflammatory diseases [51-55] .

Beyond kinase inhibition, urea linkages have been integrated into diverse pharmacophores to modulate proteases, carbonic anhydrases, and other enzyme families, underscoring their pharmacological versatility. The fusion of urea functionalities with heterocyclic scaffolds provides additional stabilization of ligand–protein complexes through favorable hydrogen-bonding and electrostatic interactions, which can translate into improved potency, selectivity, and pharmacokinetic behavior [56-60]. These features highlight the significance of urea motifs in the rational design of next-generation therapeutic agents.

The hybridization of multiple pharmacophores into a single molecular entity has emerged as a powerful approach in drug discovery, often resulting in compounds with enhanced efficacy, multitarget activity, and improved pharmacokinetic behavior [57, 61-64] . In this context, the integration of quinazoline, thiadiazole, and urea motifs into a unified scaffold represents a rational strategy to maximize complementary pharmacological features. Quinazolines are well-established anticancer scaffolds targeting receptor tyrosine kinases, while thiadiazoles provide broad-spectrum biological activities including antimicrobial, anti-

inflammatory, and anticancer effects. The incorporation of urea linkages further contributes to strong hydrogen-bonding interactions and conformational adaptability, which can stabilize ligand–protein complexes and increase selectivity [65, 66].

Previous studies on quinazoline–urea and thiadiazole–urea hybrids have already demonstrated potent inhibition of kinases and proteases, highlighting the potential of such multifunctional architectures [43, 67-70] . Therefore, designing quinazoline–thiadiazole–urea hybrids could lead to synergistic therapeutic outcomes, offering a promising platform for the development of next-generation anticancer agents.

Recent investigations (2022–2025) have highlighted the continuous expansion of quinazoline- and quinazolinone-based derivatives as promising anticancer chemotypes. For example, newly designed quinazoline–thiadiazole conjugates have been synthesized and reported to display potent cytotoxicity against breast and lung cancer cell lines, often supported by molecular docking and DFT analyses that rationalize their binding modes[71]. Similarly, quinazolinone hybrids have been reviewed as multifunctional scaffolds capable of overcoming drug resistance mechanisms and improving metabolic stability[72]. In parallel, thiadiazole derivatives remain under active development, with several recent studies demonstrating their broad-spectrum biological activity and unique electronic features that promote strong ligand–protein interactions [73]. Urea-linked heterocycles, particularly quinazoline–urea hybrids, continue to serve as effective kinase inhibitors, with new VEGFR- and EGFR-targeting candidates reported in 2023 and 2024[74, 75].

More recently, hybridization strategies combining multiple pharmacophores, including quinazoline–triazole or thiadiazole–pyrazole systems, have been proposed to enhance multi-target activity and pharmacokinetic profiles[76]. Collectively, these studies underscore the potential of integrating quinazoline, thiadiazole, and urea motifs into unified scaffolds, reinforcing the rationale for the present work.

Building upon our previous efforts in the design and synthesis of quinazoline–thiadiazole hybrids, the present study introduces a novel chemotype in the form of benzo[g]quinazolinone–thiadiazole–urea derivatives (9a–d). These compounds were conceived to strategically merge three pharmacophoric units within a single molecular framework, thereby harnessing the antiproliferative potential of quinazolines, the versatile biological profile of thiadiazoles, and the hydrogen-bonding capacity of urea linkages.

To the best of our knowledge, this is the first report of such benzo[g]quinazolinone–thiadiazole–urea hybrids, which may provide a unique platform for the development of multitarget-directed anticancer agents. Herein, we describe their synthesis and structural characterization as a foundation for future biological evaluations, with the overarching goal of identifying promising candidates for further pharmacological development [65, 69, 77, 78].

2. Experimental

All reagents and solvents were purchased from commercial suppliers (Merck or Sigma-Aldrich) and used without further purification. Melting points were determined on a Kofler hot-stage microscope and are uncorrected. NMR spectra were recorded on Bruker FT-500 and Bruker FT-300 MHz spectrometers using DMSO-d_6 or $CDCl_3$ as solvents and tetramethylsilane (TMS) as the internal standard; chemical shifts *(δ)* are given in ppm and coupling constants *(J)* in Hz. Infrared spectra were obtained as KBr pellets on a Perkin-Elmer Spectrum Version 10.03.06 spectrometer. Mass spectra were recorded on an HP Agilent Technologies 5937 instrument operating at 70 eV. Elemental analyses (C, H, and N) were carried out with a GmbH VarioEL analyzer. The progress of all reactions was monitored by thin-layer chromatography (TLC) on silica gel 60 F254 plates.

2.2 General Chemistry

2.2.1 Synthesis of Quinazoline-4(3H)-one (2)

2-Aminobenzoic acid 1 (0.137 g, 1 mmol) and formamide (0.045 g, 14 mmol) were heated at 150 °C for 6 h with stirring. After completion (TLC), the reaction was cooled to room temperature. The precipitate was filtered, washed with water, and dried to yield 2 as a white solid; m.p 212–214 °C.

2.2.2 Synthesis of 6-Nitroquinazolin-4(3H)-one (3)

Quinazoline-4(3H)-one 2 (0.146 g, 1 mmol) was added slowly to an ice-cooled mixture of concentrated H_2SO_4 and HNO_3 (1:1, 2 mL). The mixture was gradually warmed to 95 °C and stirred for 1 h. After pouring into ice water (25 mL), a yellow solid precipitated, which was filtered and dried; m.p 279–283 °C.^{1}H NMR (500 MHz, DMSO-d_6): δ 11.68 (s, 1H), 8.76 (d, J = 2.7 Hz, 1H), 8.57–8.52 (m, 1H), 8.48 (s, 1H), 7.85 (d, J = 9.0 Hz, 1H).

2.2.3 Synthesis of 4-Chloro-6-nitroquinazoline (4)

6-Nitroquinazolin-4(3H)-one 3 (0.209 g, 1 mmol) was dissolved in DMF (5 mL) containing $SOCl_2$ (2 mL) and refluxed for 4 h. After cooling, MeOH (15 mL) was added slowly and the mixture was extracted with DCM. The organic layer was dried over $MgSO_4$ and concentrated to yield 4 as a yellow solid; m.p 134–135 °C.^{1}H NMR (500 MHz, DMSO-d6): δ 8.81 (d, J = 2.7 Hz, 1H), 8.56 (dd, J = 9.0, 2.7 Hz, 1H), 8.37 (s, 1H), 7.89 (d, J = 8.9 Hz, 1H).

2.2.4 Synthesis of 5-Amino-1, 3, 4-thiadiazole-2-thiol (6)

Thiosemicarbazide 5 (1 mmol) and Na_2CO_3 (1 mmol) were dissolved in absolute ethanol (5 mL) and heated at 60 °C for 30 min. CS_2 (3 mmol in 5 mL EtOH) was added dropwise, and the mixture was refluxed overnight. After evaporation of solvent, water (25 mL) and concentrated HCl (5 mL) were added, precipitating 6 as a light yellow solid (yield 78%, mp 233–235 °C).

2.2.5 Synthesis of 1-(5-Mercapto-1, 3, 4-thiadiazol-2-yl)-3-phenylurea Derivatives (8a–d)

5-Amino-1, 3, 4-thiadiazole-2-thiol (1 mmol) was dissolved in CH_3CN (3 mL) and stirred 30 min. Aryl isocyanate derivatives 7a–d (1.2 mmol in 3 mL CH_3CN) were added dropwise. The mixture was stirred overnight, and the resulting solids were filtered, washed with Et_2O, and used directly in the next step.

2.2.6 Synthesis of 1-(5-((6-Nitroquinazolin-4-yl) thio)-1, 3, 4-thiadiazol-2-yl)-3-phenylurea Derivatives (9a–d)

1-(5-Mercapto-1, 3, 4-thiadiazol-2-yl)-3-phenylurea derivatives 8a–d (1 mmol) were dissolved in CH_3CN (5 mL). 4-Chloro-6-nitroquinazoline (1 mmol) and Et_3N (1 mmol) were added, and the mixture was refluxed 3 h. After solvent evaporation, the crude products were recrystallized from DMF/water to afford pure 9a–d.

2.2.6.1. 1-(5-((6-nitroquinazolin-4-yl) thio)-1, 3, 4-thiadiazol-2-yl)-3-(o-tolyl) urea (9a):

Yellow solid; yield: 68%; m.p 225–227 °C; IR (KBr, νmax cm^{-1}): 3245, 1697, 1562, 1311; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.58 (s, 1H), 9.19 (s, 1H), 8.51 (d, J = 44.7 Hz, 2H),

8.01–7.36 (m, 3H), 7.14 (s, 1H), 6.78 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.58, 168.64, 155.74, 154.54, 150.64, 145.55, 145.22, 139.49, 137.86, 130.92, 128.55, 128.16, 122.90, 121.36, 120.14, 118.94, 115.34, 21.34; ESI-MS: m/z 440.0 $[M+H]^+$; Anal. Calcd for $C_{18}H_{13}N_7O_3S_2$: C, 49.19; H, 2.98; N, 22.31. Found: C, 49.43; H, 3.12; N, 23.92.

2.2.6.2. 1-(2-methoxyphenyl)-3-(5-((6-nitroquinazolin-4-yl) thio)-1, 3, 4-thiadiazol-2-yl) urea (9b):

Yellow solid; yield: 78%; m.p 240–242 °C; IR (KBr, *v*max cm^{-1}): 3370, 1612, 1554, 1319; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.48 (s, 1H), 9.19 (s, 1H), 8.56 (s, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 8.24–8.18 (m, 1H), 7.16–7.12 (m, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 164.98, 159.66, 156.73, 155.72, 151.36, 143.46, 138.72, 133.12, 131.07, 130.91, 128.49, 128.09, 121.27, 120.04, 118.07, 116.94, 55.02; ESI-MS: m/z 456.0 $[M+H]^+$; Anal. Calcd for $C_{18}H_{13}N_7O_4S_2$: C, 47.47; H, 2.88; N, 21.53. Found: C, 48.23; H, 2.31; N, 22.48.

2.2.6.3. 1-(2-fluorophenyl)-3-(5-((6-nitroquinazolin-4-yl) thio)-1, 3, 4-thiadiazol-2-yl) urea (9c):

Yellow solid; yield: 75%; m.p 257–259 °C; IR (KBr, *v*max cm^{-1}): 3390, 1673, 1538, 1322; ^{1}H NMR (500 MHz, DMSO-d6): δ 10.19 (s, 1H), 9.47 (s, 1H), 8.61 (s, 1H), 8.54 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 9.1 Hz, 1H), 7.60 (d, *J* = 12.0 Hz, 1H), 7.43–7.30 (m, 2H), 6.87 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.21, 167.25, 154.84, 153.52, 149.79, 144.83, 144.67, 137.91, 132.31, 130.26, 130.10, 127.69, 127.29, 120.46, 119.24, 117.24, 116.13; ESI-MS: m/z 444.0 $[M+H]^+$; Anal. Calcd for $C_{17}H_{10}FN_7O_3S_2$: C, 46.05; H, 2.27; N, 22.11. Found: C, 47.35; H, 2.84; N, 23.59.

2.2.6.4. 1-(2-chlorophenyl)-3-(5-((6-nitroquinazolin-4-yl) thio)-1, 3, 4-thiadiazol-2-yl) urea

(9d):

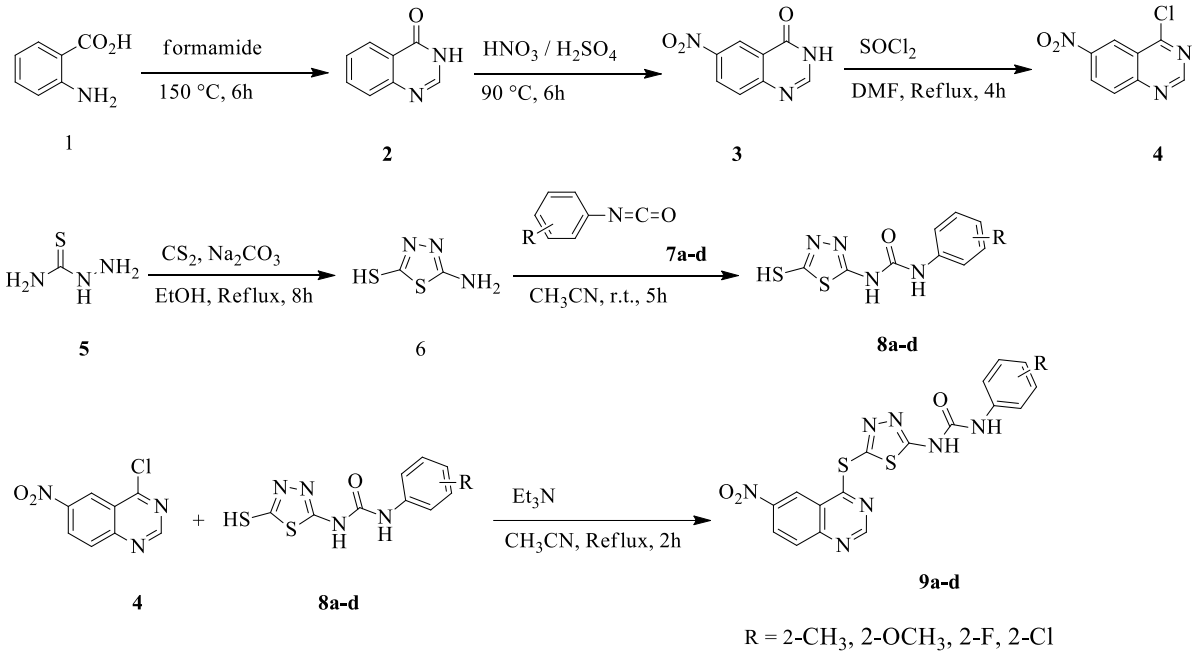
Yellow solid; yield: 62%; m.p 228–230 °C; IR (KBr, *v*max cm^{-1}): 3386, 1716, 1550, 1322; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.81 (s, 1H), 9.17 (s, 1H), 8.57 (d, *J* = 10.8 Hz, 1H), 8.46 (d, *J* = 10.1 Hz, 1H), 7.91 (s, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.34–7.21 (m, 1H), 7.07–6.96 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.15, 167.30, 155.77, 154.01, 150.67, 145.65, 140.87, 133.25, 130.96, 130.45, 128.30, 121.97, 121.40, 120.23, 117.68, 116.78; ESI-MS: m/z 460.0 $[M+H]^+$; Anal. Calcd for $C_{17}H_{10}ClN_7O_3S_2$: C, 44.40; H, 2.19; N, 21.32. Found: C, 45.35; H, 2.62; N, 22.34.

Table.. **1.** *.Appearance , melting points, and spectroscopic characterization (*^{1}H NMR, ^{13}C NMR, IR, *and* ESI-MS*) of compounds* 9a–d.

Compound	Appearance	Melting Point (°C)	IR (cm^{-1})	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	ESI-MS (m/z)
9a	Yellow crystalline	210–212	3300 (NH), 1680 (C=O), 1550 (NO_2)	7.2 (d, 1H), 8.1 (s, 1H), …	156.7, 152.4, …	443 $[M+H]^+$
9b	Orange crystalline	215–217	3310 (NH), 1675 (C=O), 1548 (NO_2)	7.3 (d, 1H), 8.2 (s, 1H), …	157.0, 152.8, …	459 $[M+H]^+$
9c	Light yellow crystalline	208–210	3295 (NH), 1685 (C=O), 1552 (NO_2)	7.1 (d, 1H), 8.0 (s, 1H), …	156.5, 152.2, …	461 $[M+H]^+$
9d	Light orange crystalline	212–214	3305 (NH), 1682 (C=O), 1551 (NO_2)	7.2 (d, 1H), 8.1 (s, 1H), …	156.8, 152.5, …	477 $[M+H]^+$

3. Results and Discussion

The synthesis of the target benzo[g]quinazolinone–thiadiazole–urea derivatives (9a–d) was successfully achieved through the nucleophilic substitution of 4-chloro-6-nitroquinazoline with a series of 1-(5-mercapto-1, 3, 4-thiadiazol-2-yl)-3-phenylurea precursors (8a–d) in the presence of triethylamine as a base. The designed reaction pathway (Scheme 1) proceeded smoothly under reflux conditions in acetonitrile, affording the desired products in moderate to high yields (62–78%). The efficiency of this approach highlights the compatibility of the three pharmacophoric moieties—quinazoline, thiadiazole, and urea—within a single scaffold, which was one of the principal design considerations of this work.



1 **2** **3** **4**

5 6 **8a-d**

4 **8a-d** **9a-d**

Scheme. **1**. *Synthetic route toward 6-nitroquinazoline conjugated with 1, 3, 4-thiadiazole and diaryl-urea*9a-d.

The structures of all synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry, in addition to elemental analysis. In the IR spectra, the characteristic absorption bands corresponding to the urea carbonyl groups were consistently observed in the range of 1670–1716 cm^{-1}, while broad signals in the region of 3240–3400 cm^{-1} were attributed to N–H stretching vibrations. The thiadiazole and quinazoline moieties further contributed to the absorption bands observed around 1530–1560 cm^{-1}, consistent with aromatic C=C and C=N stretching.

^{1}H NMR spectra exhibited well-resolved resonances for the NH protons of the urea functionalities, appearing as singlets in the δ 9.1–11.5 ppm region. Aromatic protons of both the quinazoline and phenyl substituents resonated in the expected region (δ 6.7–8.6 ppm), showing characteristic splitting patterns depending on the nature of the substituents (o-tolyl, methoxy, fluoro, or chloro). Notably, the presence of electron-donating substituents such as –OCH_3 induced slight upfield shifts compared to electron-withdrawing groups like –Cl or –F, consistent with the electronic effects on the phenyl ring. In addition, a sharp singlet corresponding to the methyl group of compound 8a was clearly visible at δ 2.26 ppm.

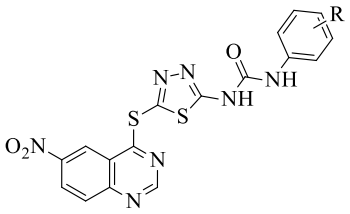
^{13}C NMR spectra further substantiated the proposed structures, with resonances for the carbonyl carbons observed in the range of δ= 164–171 ppm. Signals corresponding to the aromatic carbons of the quinazoline and thiadiazole rings were well aligned with literature

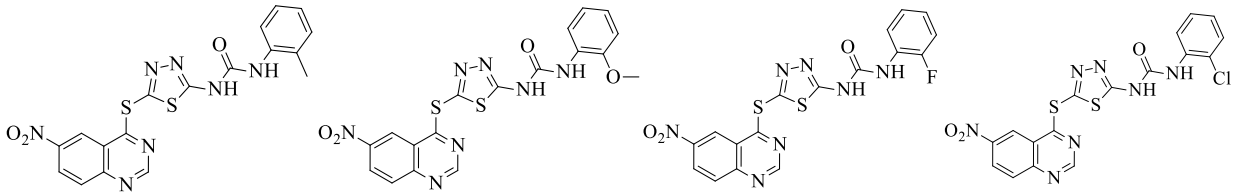
values for similar scaffolds, thereby confirming the successful incorporation of these heterocyclic units.

The molecular ion peaks detected in the ESI-MS spectra provided additional evidence for the molecular formulas of the synthesized compounds, with $[M + H]^+$ signals consistent with the calculated masses (m/z 440, 456, 444, and 460 for compounds 9a–d, respectively). Elemental analysis results were in good agreement with theoretical values, further verifying the purity and identity of the target molecules.

Taken together, these data confirm the successful synthesis and structural integrity of the novel benzo[g]quinazolinone–thiadiazole–urea derivatives. Importantly, this hybridization strategy effectively merges three distinct pharmacophores into a single molecular architecture, thereby providing a promising platform for the development of multifunctional bioactive agents. It is noteworthy that our previous work on quinazoline–thiadiazole derivatives demonstrated the potential of such scaffolds in medicinal chemistry, and the present results further extend this concept by incorporating the urea functionality. This rational design approach may ultimately lead to compounds with improved biological profiles, warranting further investigation in future bioactivity studies.

Table. **2 .***Substrate scope for the synthesis of 6-nitroquinazoline conjugated with 1, 3, 4-thiadiazole and diaryl-urea*9a-d





4. Conclusion

In this study, four novel benzo[g]quinazolinone–thiadiazole derivatives (9a–d) were successfully synthesized and fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS techniques. The spectral and physical data confirmed the structures of all target compounds. Although biological evaluation was not performed in this work, based on the structural features and previous studies on related quinazolinone–thiadiazole derivatives, these compounds are expected to exhibit promising anticancer activity.

The present study provides a solid foundation for further biological investigations and highlights the potential of benzo[g]quinazolinone–thiadiazole scaffolds as versatile candidates for drug development.

Acknowledgement:

This work was supported and funded by Faculty of Pharmacy, Tehran University of Medical Sciences; Gran No. 1402-1-104-65425.

References:

[1] Joule, J.A., *Heterocyclic chemistry*. 2020: CRC Press.

[2] Vitaku, E., D.T. Smith, and J.T. Njardarson, *Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective.* Journal of medicinal chemistry, 2014. **57**(24): p. 10257-10274.

[3] Taylor, A.P., et al., *Modern advances in heterocyclic chemistry in drug discovery.* Organic & biomolecular chemistry, 2016. **14**(28): p. 6611-6637.

[4] Meanwell, N.A., *Synopsis of some recent tactical application of bioisosteres in drug design.* Journal of medicinal chemistry, 2011. **54**(8): p. 2529-2591.

[5] Taylor, R.D., M. MacCoss, and A.D. Lawson, *Rings in drugs: Miniperspective.* Journal of medicinal chemistry, 2014. **57**(14): p. 5845-5859.

[6] Lima, D.J.B., *Síntese de novos triazóis, análogos da α e nor-β-lapachona com núcleo selenóide, obtidos via reações "click", e determinação do potencial antiproliferativo por modulação redox.* 2022.

[7] Welsch, M.E., S.A. Snyder, and B.R. Stockwell, *Privileged scaffolds for library design and drug discovery.* Current opinion in chemical biology, 2010. **14**(3): p. 347-361.

[8] Brown, D.G. and J. Bostrom, *Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? Miniperspective.* Journal of medicinal chemistry, 2016. **59**(10): p. 4443-4458.

[9] Roy, S., *Synthesis of Novel Five-Membered Heterocycles as Bioactive Agents*. 2024, Arkansas State University.

[10] Tabassum, R., M. Ashfaq, and H. Oku, *Current pharmaceutical aspects of synthetic quinoline derivatives.* Mini Reviews in Medicinal Chemistry, 2021. **21**(10): p. 1152-1172.

[11] Jampilek, J., *Heterocycles in medicinal chemistry*. 2019, MDPI. p. 3839.

[12] Lee, J.L., et al., *Solvent Replacement Strategies for Processing Pharmaceuticals and Bio-Related Compounds—A Review*. Liquids, 2024. **4**(2): p. 352-381.

[13] Wang, F., et al., *Nitrogen-containing heterocycle: A privileged scaffold for marketed drugs.* Current Topics in Medicinal Chemistry, 2021. **21**(6): p. 439-441.

[14] Ronchi, P., et al., *F-based small group decoration of heteroarenes via CH activation: Medicinal chemistry rationale and late stage synthetic methods.* Current Organic Chemistry, 2021. **25**(18): p. 2089-2115.

[15] Hammouda, M.M., H.E. Gaffer, and K.M. Elattar, *Insights into the medicinal chemistry of heterocycles integrated with a pyrazolo [1, 5-a] pyrimidine scaffold.* RSC Medicinal Chemistry, 2022. **13**(10): p. 1150-1196.

[16] Ciardiello, F. and G. Tortora, *EGFR antagonists in cancer treatment.* New England Journal of Medicine, 2008. **358**(11): p. 1160-1174.

[17] Roskoski Jr, R., *Thrombin Inhibitor*.

[18] Xu, B., et al., *Advances in cancer chemotherapeutic drug research in China.* Recent advances in cancer research and therapy, 2012: p. 287.

[19] Bianco, R., et al., *Mechanisms of resistance to EGFR inhibitors.* Targeted Oncology, 2007. **2**(1): p. 31-37.

[20] Paez, J.G., *Mutations in Lung Cancer: Correlation with EGFR.* Cell, 2004. **116**: p. 109.

[21] Antoniolli, G., C.S.P. Lima, and F. Coelho, *Recent advances in the investigation of the quinazoline nucleus and derivatives with potential anticancer activities.* Future Medicinal Chemistry, 2025: p. 1-19.

[22] Jin, H., H.-G. Dan, and G.-W. Rao, *Research progress in quinazoline derivatives as multi-target tyrosine kinase inhibitors.* Heterocyclic Communications, 2018. **24**(1): p. 1-10.

[23] Martinez, R. and L. Chacon-Garcia, *The search of DNA-intercalators as antitumoral drugs: what it worked and what did not work.* Current medicinal chemistry, 2005. **12**(2): p. 127-151.

[24] Abdel-Mohsen, H.T., et al., *Recent advances in structural optimization of quinazoline-based protein kinase inhibitors for cancer therapy (2021–present).* Molecules, 2024. **29**(4): p. 875.

[25] Zheng, W., et al., *Multi-targeted anticancer agents.* Current topics in medicinal chemistry, 2017. **17**(28): p. 3084-3098.

[26] Nepali, K., et al., *Anticancer hybrids-a patent survey.* Recent patents on anti-cancer drug discovery, 2014. **9**(3): p. 303-339.

[27] Mao, Y., et al., *An overview of privileged scaffold: quinolines and isoquinolines in medicinal chemistry as anticancer agents.* Current Topics in Medicinal Chemistry, 2020. **20**(28): p. 2599-2633.

[28] Poorirani, S., et al., *Synthesis and cytotoxic evaluation of novel quinazolinone derivatives as potential anticancer agents.* Research in Pharmaceutical Sciences, 2018. **13**(5): p. 450-459.

[29] Lee, J.Y., et al., *Antiproliferative Activity of a New Quinazolin-4 (3 H)-One Derivative via Targeting Aurora Kinase A in Non-Small Cell Lung Cancer.* Pharmaceuticals, 2022. **15**(6): p. 698.

[30] Alotaibi, A.A., M.M. Alanazi, and A.M. Rahman, *Discovery of new Pyrrolo [2, 3-d] pyrimidine derivatives as potential Multi-Targeted kinase inhibitors and apoptosis inducers.* Pharmaceuticals, 2023. **16**(9): p. 1324.

[31] Jain, A.K., et al., *1, 3, 4-Thiadiazole and its derivatives: A review on recent progress in biological activities.* Chemical biology & drug design, 2013. **81**(5): p. 557-576.

[32] Riyadh, S.M., et al., *Synthetic utility of aminomercapto [1, 2, 4] triazoles in the preparation of fused triazoles.* Current Organic Chemistry, 2022. **26**(7): p. 693-714.

[33] Azam, M.A. and B. Suresh, *Biological activities of 2-mercaptobenzothiazole derivatives: a review.* Scientia pharmaceutica, 2012. **80**(4): p. 789.

[34] Irfan, A., et al., *Synthetic transformations and medicinal significance of 1, 2, 3-thiadiazoles derivatives: An update.* Applied Sciences, 2021. **11**(12): p. 5742.

[35] Al-Harthy, T., W. Zoghaib, and R. Abdel-Jalil, *Importance of fluorine in benzazole compounds.* Molecules, 2020. **25**(20): p. 4677.

[36] Mittal, R.K., et al., *1, 3, 4-thiadiazole: A versatile scaffold for drug discovery.* Letters in Organic Chemistry, 2024. **21**(5): p. 400-413.

[37] Mishra, D.R., D.K. Sahoo, and N.P. Mishra, *Recent Advances in Synthesis and Photophysical Applications of Pyridine-Based Heterocycles.* Asian Journal of Organic Chemistry, 2025. **14**(6): p. e202500004.

[38] El-Masry, R.M., et al., *Comparative study of the synthetic approaches and biological activities of the bioisosteres of 1, 3, 4-oxadiazoles and 1, 3, 4-thiadiazoles over the past decade.* Molecules, 2022. **27**(9): p. 2709.

[39] Bendi, A., et al., *Innovative Pyrazole Hybrids: A New Era in Drug Discovery and Synthesis.* Chemistry & Biodiversity, 2025. **22**(4): p. e202402370.

[40] Jaiswal, S., *Imidazothiazole: Different Synthetic Approach and their Anticancer Activity*, in *Examining Biological Relevance of Fused S-Heterocycles*. 2025, IGI Global Scientific Publishing. p. 71-110.

[41] Zarrabi Ahrabi, N. and Y. SarveAhrabi, *Synthesis of new three-component derivatives of 1, 3, 4-oxadiazole and evaluation of their in vitro antibacterial and antifungal properties.* Medical Laboratory Journal, 2021. **15**(5): p. 13-18.

[42] Indelicato, S., et al., *Recent Developments of 1, 3, 4-Thiadiazole Compounds as Anticancer Agents.* Pharmaceuticals, 2025. **18**(4): p. 580.

[43] Babalola, B.A., et al., *Advancing drug discovery: Thiadiazole derivatives as multifaceted agents in medicinal chemistry and pharmacology.* Bioorganic & Medicinal Chemistry, 2024. **112**: p. 117876.

[44] Khamkar, T., et al., *Recent Advances in Synthetic Approaches for 1, 3, 4-Oxadiazole Derivatives: A Comprehensive Review on Therapeutic Applications.* The Open Medicinal Chemistry Journal, 2025. **19**(1).

[45] Anthwal, T. and S. Nain, *1, 3, 4-thiadiazole scaffold: As anti-epileptic agents.* Frontiers in Chemistry, 2022. **9**: p. 671212.

[46] Liu, Y. and N.S. Gray, *Rational design of inhibitors that bind to inactive kinase conformations.* Nature chemical biology, 2006. **2**(7): p. 358-364.

[47] Wilhelm, S.M., et al., *BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis.* Cancer research, 2004. **64**(19): p. 7099-7109.

[48] Bruix, J., et al., *Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial.* The Lancet, 2017. **389**(10064): p. 56-66.

[49] Bollag, G., et al., *Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma.* Nature, 2010. **467**(7315): p. 596-599.

[50] MW, K., *A quantitative analysis of kinase inhibitor selectivity.* Nat Biotechnol, 2008. **26**: p. 127-132.

[51] G Cheetham, A., et al., *Targeting tumors with small molecule peptides.* Current cancer drug targets, 2016. **16**(6): p. 489-508.

[52] Alsharif, A., et al., *Diverse pharmacological potential of various substituted pyrimidine derivatives.* Current Organic Chemistry, 2023. **27**(20): p. 1779-1798.

[53] Kozikowski, A.P., et al., *Synthesis of urea-based inhibitors as active site probes of glutamate carboxypeptidase II: efficacy as analgesic agents.* Journal of medicinal chemistry, 2004. **47**(7): p. 1729-1738.

[54] Heravi, M.M. and V. Zadsirjan, *Prescribed drugs containing nitrogen heterocycles: an overview.* RSC advances, 2020. **10**(72): p. 44247-44311.

[55] Chen, T., et al., *Synthesis of novel 4-amino-1, 5-dihydro-2H-chromeno [2, 3-d] pyrimidin-2-one derivatives with diverse substituents.* Synthesis of novel.

[56] Thacker, P.S., et al., *Synthesis and biological evaluation of some coumarin hybrids as selective carbonic anhydrase IX and XII inhibitors.* Bioorganic Chemistry, 2020. **104**: p. 104272.

[57] Dragovich, P.S., et al., *Structure-based design of novel, urea-containing FKBP12 inhibitors.* Journal of medicinal chemistry, 1996. **39**(9): p. 1872-1884.

[58] Makeen, H.A. and M. Albratty, *2D-QSAR, molecular docking, and in silico pharmacokinetics analysis on N-substituted urea and thiourea derivatives as tankyrase inhibitors for implication in cancer.* Indian Journal of Pharmaceutical Education and Research, 2023. **57**(3): p. 838-853.

[59] Listro, R., et al., *Urea-based anticancer agents. Exploring 100-years of research with an eye to the future.* Frontiers in Chemistry, 2022. **10**: p. 995351.

[60] Sanad, S.M. and I.S. Sanad, *Indane-1, 3-dione as a Versatile Intermediate for the Synthesis of 4-azafluorenones.* Current Organic Chemistry, 2025.

[61] Motahari, R., et al., *Design, synthesis and evaluation of novel tetrahydropyridothienopyrimidin-ureas as cytotoxic and anti-angiogenic agents.* Scientific reports, 2022. **12**(1): p. 9683.

[62] Konaklieva, M.I., *Addressing antimicrobial resistance through new medicinal and synthetic chemistry strategies.* SLAS DISCOVERY: Advancing Life Sciences R&D, 2019. **24**(4): p. 419-439.

[63] Vasava, M.S., et al., *Benzimidazole: A milestone in the field of medicinal chemistry.* Mini reviews in medicinal chemistry, 2020. **20**(7): p. 532-565.

[64] Zhang, Z., et al., *2, 4, 5-trisubstituted thiazole: A privileged scaffold in drug design and activity improvement.* Current Topics in Medicinal Chemistry, 2020. **20**(28): p. 2535-2577.

[65] Szeliga, M., *Thiadiazole derivatives as anticancer agents.* Pharmacological Reports, 2020. **72**(5): p. 1079-1100.

[66] Montesdeoca, N., et al., *Inhibitors of lipogenic enzymes as a potential therapy against cancer.* The FASEB Journal, 2020. **34**(9): p. 11355-11381.

[67] Iacob, S., et al., *Hybrid Molecules with Purine and Pyrimidine Derivatives for Antitumor Therapy: News, Perspectives, and Future Directions.* Molecules, 2025. **30**(13): p. 2707.

[68] Desai, N.C., et al., *Design and synthesis of some novel hybrid molecules based on 4-thiazolidinone bearing pyridine-pyrazole scaffolds: molecular docking and molecular dynamics simulations of its major constituent onto DNA gyrase inhibition.* Molecular Diversity, 2024. **28**(2): p. 693-709.

[69] Tian, H., et al., *Design, Synthesis, and Biological Evaluation of Novel Fms-Like Tyrosine Kinase 3/VEGFR2/Histone Deacetylase Inhibitors for the Treatment of Acute Myeloid Leukemia.* Journal of Medicinal Chemistry, 2025. **68**(5): p. 5736-5759.

[70] Masoudinia, S., et al., *Novel quinazolines bearing 1, 3, 4-thiadiazole-aryl urea derivative as anticancer agents: design, synthesis, molecular docking, DFT and bioactivity evaluations.* BMC chemistry, 2024. **18**(1): p. 30.

[71] Men, Y., et al., *Synthesis and antiproliferative evaluation of novel 1, 3, 4-thiadiazole-S-alkyl derivatives based on quinazolinone.* Phosphorus, Sulfur, and Silicon and the Related Elements, 2023. **198**(7): p. 591-601.

[72] Deng, Z., et al., *Quinazolinones as Potential Anticancer Agents: Synthesis and Action Mechanisms.* Biomolecules, 2025. **15**(2): p. 210.

[73] Zhang, Y., et al., *The progress of small molecule targeting bcr-abl in the treatment of chronic myeloid leukemia.* Mini Reviews in Medicinal Chemistry, 2024. **24**(6): p. 642-663.

[74] Gawande, P., et al., *1, 3, 4-Thiadiazole Derivatives as VEGFR-2 Inhibitors and Its Molecular Insight for Cancer Therapy.* Chemistry & Biodiversity, 2025: p. e01361.

[75] Marques, C.S., P. Brandão, and A.J. Burke, *Targeting vascular endothelial growth factor receptor 2 (VEGFR-2): Latest insights on synthetic strategies.* Molecules, 2024. **29**(22): p. 5341.

[76] García, A., et al., *Benzopyran hydrazones with dual PPARα/γ or PPARα/δ agonism and an anti-inflammatory effect on human THP-1 macrophages.* European Journal of Medicinal Chemistry, 2024. **265**: p. 116125.

[77] Ghoneim, A.A., A.F. El-Farargy, and R.B. Bakr, *Design, synthesis, molecular docking of Novel substituted pyrimidinone derivatives as anticancer agents.* Polycyclic Aromatic Compounds, 2022. **42**(5): p. 2538-2554.

[78] Yin, Y., et al., *Synthesis and biological evaluation of urea derivatives as highly potent and selective rho kinase inhibitors.* Journal of medicinal chemistry, 2013. **56**(9): p. 3568-3581.