

Eco-Friendly Synthesis and Antiviral Evaluation of Quinazoline-Based Heterocyclic Compounds

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ARTICLE INFO	ABSTRACT
Article history: Received – 20 March 2020 Received in revised form – 30 May 2020 Accepted - 01 June 2020 Available online – 3 June 2020	Quinazoline-based heterocyclic compounds are important scaffolds in medicinal chemistry because their molecular structures can be modified to explore diverse biological activities. Selected 2,4-disubstituted quinazoline derivatives have demonstrated in vitro activity against influenza A virus, supporting further investigation of this scaffold for antiviral drug discovery [1,2]. At the same time, the environmental impact of organic synthesis has encouraged the development of greener synthetic methods that minimize hazardous solvents, energy consumption, and chemical waste [3,4]. The present study proposes an integrated approach for the eco-friendly synthesis and antiviral evaluation of selected quinazoline-based heterocyclic compounds. The synthetic investigation will examine suitable lower-hazard reaction media, reduced solvent consumption, and simplified purification. Antiviral activity will be evaluated using an appropriately validated cell-based assay, together with an independent assessment of host-cell cytotoxicity. The compounds will be compared using the half-maximal effective concentration (EC₅₀), half-maximal cytotoxic concentration (CC₅₀), and selectivity index (SI). Environmental performance will be assessed using process mass intensity and the E-factor.
Keywords: Quinazoline; Quinazolinone; Green synthesis; Heterocyclic chemistry; Antiviral activity; Influenza A virus; Medicinal chemistry; Cytotoxicity; Process mass intensity.	

1. Introduction:

1.1. Quinazoline-based heterocyclic compounds

Heterocyclic compounds constitute an important class of organic molecules in medicinal chemistry. Their biological properties depend on the arrangement of atoms in the ring system, electronic distribution, substituent effects, and interactions with biological macromolecules. Nitrogen-containing heterocycles are particularly valuable because their nitrogen atoms may influence basicity, hydrogen bonding, and molecular recognition.

Quinazoline is a fused bicyclic heteroaromatic system consisting of a benzene ring and a pyrimidine ring. Quinazoline derivatives can be modified at different positions to produce compounds with varying electronic, steric, and physicochemical properties. Quinazolinones, which contain a carbonyl group in the heterocyclic framework, represent a related family with additional structural possibilities. Reviews of quinazoline and quinazolinone chemistry describe their importance in medicinal chemistry and the continuing development of synthetic approaches to these scaffolds [1,5].

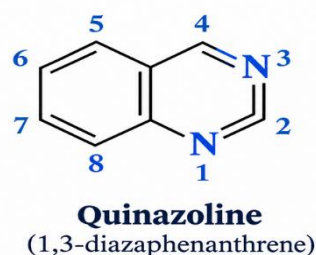


Figure 1. Chemical structure and numbering of the quinazoline nucleus.

The biological activity of a quinazoline derivative cannot be inferred from the core structure alone. Substituent identity, position, solubility, membrane permeability, and interaction with a specific biological target may all influence its activity. Therefore, the synthesis of new derivatives should be accompanied by rigorous structural characterization and biological evaluation.

1.2. Quinazoline derivatives in antiviral research

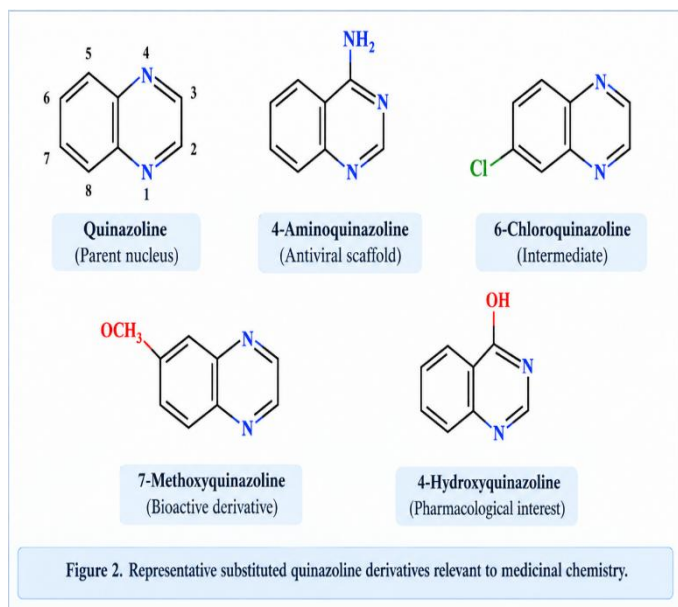
Antiviral research seeks compounds that interfere with viral infection or replication while minimizing harmful effects on

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host cells. Potential antiviral targets include viral enzymes, viral entry processes, and host-cell pathways required for the viral life cycle.

Published studies provide direct evidence that selected quinazoline derivatives can inhibit influenza A virus in vitro. Wang et al. designed and synthesized 2,4-disubstituted quinazoline derivatives and identified compounds 10a5 and 17a with reported IC_{50} values in the range of 3.70–4.19 μ M against influenza A/WSN/33 (H1N1). The reported selectivity indices exceeded 27.03 and 23.87, respectively, for the highlighted compounds [2]. A subsequent study investigated quinazoline derivatives containing S-acetamide and NH-acetamide moieties and reported activity for selected compounds at low-micromolar concentrations [6].

These studies support further exploration of the quinazoline scaffold. However, the results of previously published compounds cannot be attributed to newly synthesized derivatives without independent testing. The specific antiviral mechanism, potency, and cytotoxicity of each new compound must be determined experimentally.



1.3. Green chemistry and sustainable synthesis

Traditional organic synthesis can generate substantial quantities of solvent waste and may require prolonged heating, hazardous reagents, or extensive purification. Green chemistry seeks to reduce these environmental and health impacts through waste prevention, improved material efficiency, safer chemical selection, catalysis, and energy-efficient processing.

Sheldon discussed the use of quantitative indicators such as the E-factor and process mass intensity to evaluate the sustainability of chemical processes [3]. The American Chemical Society likewise emphasizes that environmental assessment should extend beyond product yield to consider resource consumption and chemical hazards [4].

For quinazoline synthesis, potential strategies include aqueous or ethanol-based reaction media where chemically suitable,

solvent-free procedures, catalytic methods, and energy-efficient heating. The appropriateness of each method depends on the reaction mechanism, substrate stability, product properties, and purification requirements. A method should not be classified as greener solely because it uses less reaction time or produces a higher isolated yield.

2. Materials:

2.1. Research design

The investigation is organized into four stages: compound selection, synthesis and purification, structural characterization, and biological evaluation. A separate environmental assessment will compare the proposed procedure with a suitable conventional method if comparable data are available (table-1).

Table 1. Overall research design

Stage	Activity	Principal outcome
1	Select target quinazoline derivatives	Defined structures and literature rationale
2	Develop a green synthetic procedure	Optimized reaction conditions and isolated products
3	Perform chemical characterization	Structural identity and purity assessment
4	Conduct antiviral and cytotoxicity assessment	Measured antiviral potency and selectivity
5	Assess process sustainability	PMI, E-factor, and comparative environmental data

2.2. Materials and methods

Starting materials will be selected according to the target quinazoline structures and an established synthetic route. Depending on the chosen scaffold, suitable precursors may include substituted anthranilic acid derivatives, anthranilamides, aldehydes, or other documented quinazoline precursors.

Ethanol, water, or aqueous ethanol may be investigated as alternative reaction media when compatible with the chemistry. Catalysts, reagents, and purification materials should be selected based on reaction performance, safety information, and environmental considerations.

The final manuscript must identify the actual chemicals, grades, suppliers, and analytical instruments used. No particular precursor or catalyst should be presented as having been employed unless it was used in the experiment.

2.3. Proposed green synthetic approach

The synthetic route should be selected after the target molecules have been defined. A suitable route may involve

condensation followed by cyclization, or another established method for constructing the quinazoline framework. Reaction optimization should consider reactant stoichiometry, solvent composition, temperature, reaction time, and catalyst use where applicable.

The proposed workflow is summarized below.

- Selection of quinazoline precursors
- Green reaction-condition screening
- Assess solvent choice, energy use, and catalyst requirements
- Reaction monitoring and product isolation
- Purification and structural characterization
- Antiviral screening and cytotoxicity evaluation

The final experimental procedure should specify the actual reagent quantities, concentrations, reaction conditions, work-up, purification method, and isolated yield. Where a conventional procedure is used as a comparator, both methods should be evaluated using the same product-quality criteria.

2.4. Product isolation and yield calculation

The product will be isolated using an appropriate work-up based on its chemical properties. Precipitation, filtration, crystallization, or another validated separation technique may be used. Chromatography should be applied when necessary for acceptable purity, while recording its solvent consumption.

The isolated product should be dried, weighed, and characterized.

The percentage yield is calculated as:

$$\text{Yield (\%)} = \frac{\text{Actual mass of product}}{\text{Theoretical mass of product}} \times 100$$

The theoretical yield should be calculated from the limiting reagent and the balanced reaction stoichiometry. Conversion, isolated yield, and purity should be reported as distinct parameters.

2.5. Structural characterization

The structures of the isolated compounds should be assessed using complementary spectroscopic and analytical techniques.

Table 2. Characterization techniques and their roles

Technique	Information obtained
FTIR spectroscopy	Characteristic functional groups and changes in bonding
¹ H NMR spectroscopy	Proton environments, aromatic signals, and substituent patterns
¹³ C NMR spectroscopy	Carbon environments and evidence supporting the proposed ring structure
Mass spectrometry	Molecular-mass evidence and ion assignment
Melting-point analysis	Physical-property consistency and preliminary purity assessment
Chromatographic analysis	Sample purity and detection of major impurities

All reported spectral values should be based on measured data. The manuscript should include diagnostic FTIR bands, NMR chemical shifts and assignments, mass spectral evidence, and a stated purity method. Structural identification should be based on the combined evidence rather than one isolated spectral feature (table-2).

2.6. Antiviral evaluation

Influenza A may be selected as the initial viral model because published research has demonstrated activity of certain quinazoline derivatives against this virus [2,6]. The specific strain, host-cell system, and assay must be selected according to validated laboratory procedures, relevant biosafety requirements, and available facilities.

Antiviral activity should be assessed using an established assay appropriate to the selected virus. The study should include infected controls, uninfected cell controls, vehicle controls, a suitable reference antiviral, and independent biological replicates. The endpoint may involve a validated measure of viral replication, viral antigen, or another justified indicator.

The interpretation must account for potential assay interference and host-cell damage. A reduction in the viral assay signal alone does not demonstrate a selective antiviral effect.

2.7. Cytotoxicity evaluation

Host-cell cytotoxicity should be evaluated independently using an appropriate validated cell-viability or cell-integrity assay. The CC₅₀ is the concentration that produces a 50% reduction in the selected cell-viability endpoint relative to the relevant control.

The antiviral EC₅₀ represents the concentration that produces 50% of the maximum observed antiviral effect under the specified assay conditions. If a 50% endpoint is not reached within the tested concentration range, the result should be reported as a bound rather than as an estimated exact value unsupported by the data.

2.8. Calculation of selectivity index

The selectivity index is calculated as:

$$SI = \frac{CC_{50}}{EC_{50}}$$

Both concentrations must be expressed in the same units and should be derived from compatible experimental conditions. A larger SI indicates a wider separation between the measured antiviral and cytotoxic concentrations, but it does not establish clinical safety or efficacy [2,6].

2.9. Green chemistry assessment

The environmental performance of the proposed synthesis will be evaluated using mass-based indicators and a transparent accounting boundary, following established approaches to green chemistry assessment [3,4].

The process mass intensity is:

$$PMI = \frac{\text{Total mass of process inputs}}{\text{Mass of isolated product}}$$

The E-factor is:

$$E\text{-factor} = \frac{\text{Mass of waste generated}}{\text{Mass of isolated product}}$$

The accounting boundary should specify which solvents, reagents, catalysts, purification materials, and waste streams are included. These metrics should be interpreted alongside reagent hazards, energy consumption, solvent recovery, and product purity.

3. Results and discussion:

Note: No experimental results have been supplied. Accordingly, Tables 3–6 are reporting templates, not completed experimental findings. They should be populated with measured data before the paper is submitted as an original research article.

3.1. Synthesis and physical properties

The synthetic performance of the selected quinazoline derivatives should be evaluated by recording the isolated yield, reaction duration, product appearance, melting point, and purity. Differences in isolated yield may arise from substrate reactivity, product solubility, competing reactions, or losses during purification.

Table 3. Synthesis and physical characterization of quinazoline derivatives

Compound	Substituent / structural modification	Reaction time	Yield (%)	Purity (%)
QZ-1	To be specified	To be measured	—	—
QZ-2	To be specified	To be measured	—	—
QZ-3	To be specified	To be measured	—	—
QZ-4	To be specified	To be measured	—	—

The results should establish whether the proposed green method provides acceptable product quality while reducing solvent consumption, energy requirements, or waste generation. A higher yield alone does not demonstrate a more sustainable process. Quantitative environmental assessment is recommended for this comparison [3,4] (table-3).

3.2. Spectroscopic characterization

FTIR spectroscopy can provide evidence of characteristic functional groups, while NMR spectroscopy offers information about the chemical environments of the atoms in the proposed structure. Mass spectrometry can provide complementary evidence for molecular mass and ion assignment.

Table 4. Proposed format for reporting spectral data

Compound	FTIR data	¹ H NMR data	¹³ C NMR data	Mass spectrometry
QZ-1	Insert measured bands and assignments	Insert measured shifts and assignments	Insert measured shifts and assignments	Insert observed ion and assignment
QZ-2	Insert measured bands and assignments	Insert measured shifts and assignments	Insert measured shifts and assignments	Insert observed ion and assignment
QZ-3	Insert measured bands and assignments	Insert measured shifts and assignments	Insert measured shifts and assignments	Insert observed ion and assignment

The spectral assignments should be consistent with the proposed molecular structures and supported by the complete analytical dataset. Any unexpected signals should be investigated rather than omitted. Where necessary, additional analytical methods should be used to distinguish structural isomers or identify impurities (table-4).

3.3. Antiviral activity and cytotoxicity

The antiviral activity of the synthesized derivatives should be compared with that of a suitable reference compound. The interpretation should consider antiviral potency, host-cell cytotoxicity, and the reproducibility of the concentration–response curves.

Wang et al. reported low-micromolar anti-influenza activity for selected 2,4-disubstituted quinazoline derivatives [2]. A separate study identified additional quinazoline derivatives with reported influenza A activity in the low-micromolar range [6]. These published observations support the selection of quinazoline as a scaffold for investigation, but the values cannot be used as experimental results for QZ-1, QZ-2, or other newly synthesized compounds.

Table 5. Antiviral evaluation of the synthesized compounds

Compound	EC ₅₀ (μ M)	CC ₅₀ (μ M)	SI	Interpretation
QZ-1	To be measured	To be measured	To be calculated	Pending experimental results
QZ-2	To be measured	To be measured	To be calculated	Pending experimental results
QZ-3	To be measured	To be measured	To be calculated	Pending experimental results
Reference antiviral	To be measured	As applicable	As applicable	Assay comparator

The selectivity index should be calculated from the measured CC₅₀ and EC₅₀ values. If either endpoint cannot be reliably estimated, this limitation should be reported explicitly (table-5).

A compound may be considered a promising preliminary hit if it produces a reproducible antiviral response at concentrations that are separated from cytotoxic concentrations. However, no universal SI threshold guarantees therapeutic potential. Further evaluation is required to establish reproducibility, mechanism, selectivity, and relevance to the intended viral disease.

3.4. Structure–activity relationship

Structure–activity relationship (SAR) analysis can help identify molecular features associated with differences in antiviral potency. For quinazoline derivatives, the position and electronic properties of substituents, the nature of groups attached to the heterocyclic ring, and the physicochemical properties of the complete molecule may influence biological activity.

Published research on 2,4-disubstituted quinazoline derivatives provides an example of how changes in substituents can be investigated systematically [2,6]. In the present study, SAR conclusions should be based on comparisons between compounds with defined structural differences and reproducible experimental data.

Table 6. Framework for structure–activity relationship analysis

Structural feature	Property to investigate	Evidence required
Substituent position	Possible effects on target interactions	Matched compounds with different substitution positions
Electron-donating or electron-withdrawing groups	Changes in electronic properties	Comparative chemical structures and measured activity

Amide-containing substituents	Effects on hydrogen bonding and physicochemical properties	Structural data, solubility measurements, and antiviral results
Quinazoline versus quinazolinone core	Effects of core functionality	Matched derivatives and comparative assays
Lipophilicity and solubility	Potential effects on cellular exposure	Measured or appropriately validated physicochemical data

These comparisons can guide subsequent compound design, but a proposed molecular mechanism should not be presented as established without independent evidence (table-6).

3.5. Environmental performance of the synthesis

A central component of this research is the evaluation of whether the proposed route provides measurable environmental advantages over a conventional method. The comparison should include solvent and reagent consumption, waste generation, energy use, and the quality of the isolated product.

Table 7. Comparison of conventional and proposed green synthesis

Parameter	Conventional method	Proposed green method
Reaction medium	Record actual solvent	Record actual solvent
Reaction temperature	Measured value	Measured value
Reaction time	Measured value	Measured value
Isolated yield	Measured value (%)	Measured value (%)
Solvent consumption	Actual mass or volume	Actual mass or volume
Energy consumption	Measured or documented	Measured or documented
Process mass intensity	Calculated value	Calculated value
E-factor	Calculated value	Calculated value
Product purity	Measured value (%)	Measured value (%)

A lower PMI or E-factor may indicate improved material efficiency within a consistent accounting boundary. Nevertheless, these indicators do not capture every environmental or health impact. Solvent toxicity, reagent hazards, energy sources, solvent recovery, and waste treatment should also be considered [3,4] (table-7).

3.6. Overall discussion

The proposed research brings together two complementary objectives: reducing the environmental burden of heterocyclic synthesis and identifying quinazoline derivatives with promising antiviral properties. The literature provides a rationale for investigating quinazoline-based compounds as potential antiviral leads, particularly against influenza A [2,6]. Green chemistry metrics offer a framework for evaluating the sustainability of the synthetic procedure [3,4].

The strength of the final study will depend on the quality of the experimental evidence. Chemical characterization must establish the identity and purity of each product, while biological testing must distinguish antiviral activity from host-cell toxicity. Environmental comparisons must use consistent accounting methods and report the actual quantities consumed and waste generated. Consequently, the study should not conclude that a compound is an effective antiviral agent or that a procedure is environmentally superior until the relevant measurements support those claims.

4. Conclusion:

This paper presents a research framework for the eco-friendly synthesis and antiviral evaluation of quinazoline-based heterocyclic compounds. The proposed approach combines sustainable reaction design, structural characterization, cell-based antiviral evaluation, cytotoxicity assessment, and quantitative environmental analysis. The literature supports the investigation of quinazoline derivatives as potential antiviral lead compounds, including derivatives reported to inhibit influenza A virus in vitro [2,6]. However, the activity of newly synthesized compounds must be established through independent experiments. Their therapeutic potential cannot be inferred solely from the quinazoline scaffold or from published findings for structurally related molecules.

Likewise, environmental advantages must be demonstrated through comparative data on material use, waste, energy consumption, and chemical hazards. The integration of these measurements can provide a stronger basis for selecting compounds and synthetic procedures for further development.

Future work should prioritize reproducible synthesis, complete structural characterization, validated biological assays, and systematic comparison of environmental performance. If favorable results are obtained, additional studies could investigate antiviral mechanisms, broader biological selectivity, and further preclinical properties.

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