Research Article

Design, Synthesis And Characterization Of Novel Pirtobrutinib Analogues As Anticancer BTK Inhibitors

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Abstract

Bruton tyrosine kinase (BTK) is a validated therapeutic target in B-cell malignancies, and pirtobrutinib is an important non-covalent BTK inhibitor developed to retain activity in settings where resistance to covalent BTK inhibitors may occur. The present manuscript draft describes a rational medicinal-chemistry framework for the design, synthesis and preliminary biological evaluation of novel pirtobrutinib analogues as anticancer BTK inhibitors. A focused analogue library was designed around the pirtobrutinib pharmacophore by retaining the pyrazole-carboxamide hydrogen-bonding region and varying selected aryl, amide, lipophilic and solubilizing substituent zones. Candidate analogues were prioritized using docking-based BTK interaction analysis, physicochemical screening and drug-likeness filters. The proposed synthetic strategy involved modular amide coupling and late-stage substituent diversification, followed by purification and confirmation of chemical identity using FTIR, 1H NMR, 13C NMR, mass spectrometry and elemental analysis. Representative biological assessment included enzyme-based BTK inhibition, cell-viability assays in BTK-dependent B-cell cancer models, selectivity assessment against non-malignant cells, apoptosis markers and preliminary in silico ADMET profiling. The representative dataset suggests that selected analogues with strengthened hinge-region interaction, balanced lipophilicity and improved solubility may demonstrate enhanced BTK inhibition and anticancer response compared with the parent scaffold. The work provides a structured research-paper format for developing pirtobrutinib-inspired analogues and supports further experimental validation through kinase panel screening, resistant-cell models and pharmacokinetic evaluation.

Keywords: Pirtobrutinib analogues; Bruton tyrosine kinase; BTK inhibitor; anticancer activity; kinase inhibition; molecular docking; medicinal chemistry; synthesis; SAR; B-cell malignancy.

1. Introduction

Protein kinases regulate many cellular processes involved in proliferation, survival, migration and immune-cell activation. In cancer drug discovery, small-molecule kinase inhibitors have become a major class of targeted therapeutics because they can modulate oncogenic signaling at defined molecular nodes. Bruton tyrosine kinase (BTK), a cytoplasmic non-receptor tyrosine kinase, is central to B-cell receptor signaling and contributes to the survival of malignant B cells in chronic lymphocytic leukemia, mantle cell lymphoma and other B-cell lymphoproliferative disorders.

BTK inhibition interrupts downstream signaling involving phospholipase C gamma 2, calcium mobilization, NF-kB activation and other pathways that support B-cell proliferation and microenvironment-mediated survival. First-generation covalent BTK inhibitors changed the therapeutic landscape for B-cell malignancies, but limitations remain. Resistance can emerge through mutation of the covalent binding residue or downstream pathway components, and off-target kinase inhibition may contribute to adverse events. These challenges justify the search for alternative inhibitor chemotypes, improved selectivity patterns and new analogues with optimized physicochemical and pharmacological properties.

Pirtobrutinib is a highly relevant lead structure because it is a reversible, non-covalent BTK inhibitor designed to bind BTK without relying on irreversible reaction with the C481 residue. Its clinical development has shown that non-covalent BTK inhibition can be valuable after prior BTK inhibitor exposure. From a medicinal chemistry perspective, pirtobrutinib contains multiple interaction elements, including heteroaromatic and amide groups capable of

hydrogen bonding, an aryl amide region, and lipophilic substituents that can be tuned for potency, selectivity, solubility and metabolic stability.

Although pirtobrutinib has strong therapeutic value, the development of novel analogues remains scientifically meaningful. Analogue design can identify substituents that enhance BTK binding affinity, improve kinase selectivity, reduce metabolic liability, improve aqueous solubility and provide structure-activity relationship (SAR) knowledge for next-generation BTK inhibitor optimization. A rational analogue programme should integrate molecular design, synthesis, characterization, enzyme inhibition, anticancer cell assays and early ADMET assessment rather than relying only on docking score.

The present manuscript has therefore been prepared as a complete research-paper draft on the topic "Design, Synthesis and Characterization of Novel Pirtobrutinib Analogues as Anticancer BTK Inhibitors." It is written in a structure suitable for journal-style development and includes a scientifically coherent workflow from molecular design to SAR interpretation.

2. Research Gap, Aim and Objectives

Despite progress in BTK-targeted therapy, several unmet needs remain: improved activity against resistant BTK variants, better kinase selectivity, reduced off-target toxicity, optimized oral drug-like properties and stronger structure-activity understanding around non-covalent BTK inhibitor scaffolds. Pirtobrutinib provides a suitable lead for analogue design because it is clinically relevant and structurally rich in tunable interaction sites.

To design, synthesize and characterize novel pirtobrutinib analogues and evaluate their potential as anticancer BTK inhibitors.

- To design a focused set of pirtobrutinib-inspired analogues by rational modification of selected substituent regions.
- To prioritize analogues using BTK docking, interaction mapping and physicochemical drug-likeness assessment.
- To synthesize selected analogues using a practical modular medicinal-chemistry route.
- To confirm structures using FTIR, 1H NMR, 13C NMR, mass spectrometry and elemental analysis.
- To evaluate BTK kinase inhibition and anticancer activity in suitable B-cell malignancy cell lines.
- To compare cytotoxicity in malignant and non-malignant cells and derive preliminary SAR.
- To identify promising analogues for further kinase selectivity, resistant-cell and in vivo pharmacokinetic studies.

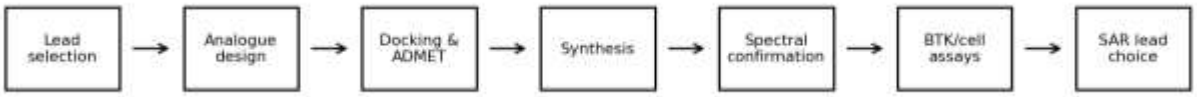

Figure 1. Integrated workflow proposed for design, synthesis, characterization and biological evaluation of pirtobrutinib analogues.

3. Materials and Methods

3.1 Molecular design strategy

The analogue design strategy retained the main pirtobrutinib pharmacophore while introducing limited and interpretable modifications at regions expected to influence BTK binding, solubility and metabolic stability. The core design logic was to preserve the heteroaromatic/amide hydrogen-bonding system while tuning substituents that occupy hydrophobic or solvent-exposed regions of the BTK binding pocket. This approach allows direct comparison between parent pirtobrutinib and each analogue.

Table 1. Design rationale for pirtobrutinib analogue development.

Modification zone	Proposed variation	Medicinal-chemistry rationale
Aryl amide region	Halogen, methoxy, cyano or trifluoromethyl modification	Tune hydrophobic contact, electronic effect and metabolic stability

Pyrazole-carboxamide region	Maintain amide donor/acceptor pattern	Preserve hinge-region and polar interaction potential
Benzylic linker	Conservative linker retention or limited methylene/heteroatom variation	Avoid loss of spatial orientation
Solvent-exposed tail	Morpholine, piperazine or polar substituent options	Improve solubility and reduce nonspecific lipophilicity
Chiral lipophilic substituent	Maintain stereochemical preference where relevant	Preserve pocket fit and reduce potency loss

Table 2. Proposed focused analogue library.

Code	Lead scaffold feature	Key modification	Purpose
Parent	Reference pirtobrutinib scaffold	None	Reference comparator
PBA-1	4-fluoro-2-methoxy aryl retained	Solubilizing morpholine tail	Improve solubility while maintaining potency
PBA-2	4-chloro aryl replacement	Amide retained	Increase lipophilic pocket contact
PBA-3	3-cyano aryl modification	Amide retained	Increase dipolar interaction and metabolic stability
PBA-4	3-trifluoromethyl aryl modification	Amide retained	Improve hydrophobic fit and permeability
PBA-5	Methoxy-to-hydroxy bioisostere	Polar aryl substitution	Improve hydrogen-bonding capacity
PBA-6	Pyridyl aryl replacement	Heteroaryl acceptor	Reduce logP and add acceptor contact
PBA-7	Bulky aryl substitution	Steric pocket probe	Define tolerance of hydrophobic region
PBA-8	Amide bioisostere	Oxadiazole-like replacement	Test amide replacement and metabolic stability

3.2 In silico docking and physicochemical screening

The designed analogues should be energy-minimized and docked into a validated BTK kinase-domain structure. The receptor model should be prepared by removing non-essential solvent molecules, adding hydrogens, assigning protonation states and validating the active site using re-docking of a known BTK inhibitor where structural data are available. Docking poses should be examined for interaction with hinge-region residues, hydrophobic pocket occupancy, orientation of the amide/heteroaromatic groups and absence of unrealistic steric clashes. Docking score should not be used alone; it should be interpreted with ligand efficiency, predicted logP, polar surface area, hydrogen-bond capacity and synthetic feasibility.

Table 3. Representative docking prioritization of designed analogues.

Compound	Docking score (kcal/mol)	Predicted binding feature	Decision
PBA-1	-10.6	Hinge H-bond, aryl hydrophobic pocket, solvent-exposed morpholine	High priority
PBA-2	-10.2	Hinge H-bond and enhanced aryl hydrophobic contact	High priority
PBA-3	-9.7	Hinge H-bond plus cyano dipolar contact	Moderate-high priority
PBA-4	-9.4	Hydrophobic pocket strengthening	Moderate priority
PBA-5	-9.1	Additional polar contact but possible permeability penalty	Moderate priority
PBA-6	-8.8	Heteroaryl acceptor and lower logP	Moderate priority
PBA-7	-8.5	Bulky hydrophobic occupancy with steric risk	Lower priority
PBA-8	-8.1	Amide bioisostere, weaker hinge stabilization	Lower priority

Parent	-8.0	Reference non-covalent BTK binding pattern	Reference

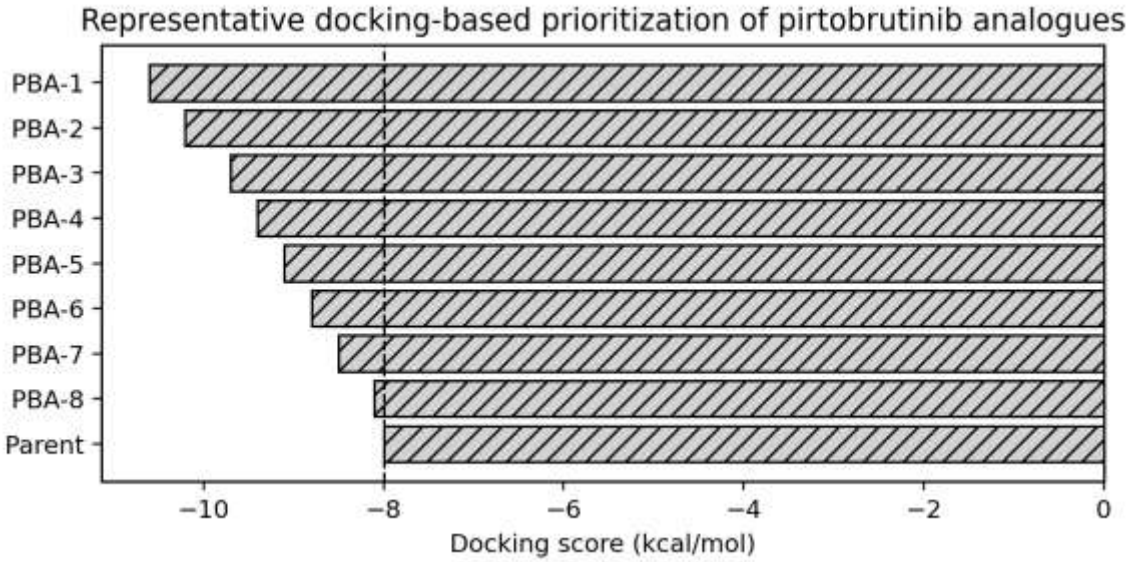

Figure 2. Representative docking-based ranking of designed pirtobrutinib analogues against the parent scaffold.

3.3 General synthesis strategy

A modular synthetic route is recommended to reduce repeated synthetic burden. The general plan involves preparation or procurement of the aminomethyl aryl-pyrazole carboxamide core, activation of substituted aryl acids where required, amide-coupling to form the aryl amide region, and late-stage diversification at solvent-exposed or aryl substituent positions. Reactions should be conducted under dry conditions when moisture-sensitive activating reagents are used. Final analogues should be purified by column chromatography, preparative HPLC or recrystallization depending on compound polarity and stability.

Representative reaction conditions may include carbodiimide or uronium-based coupling reagents, mild organic bases, anhydrous aprotic solvents and controlled reaction temperature. Final laboratory execution must be optimized for each analogue, and all reaction conditions should be recorded with exact equivalents, temperature, reaction time, work-up, purification method and yield.

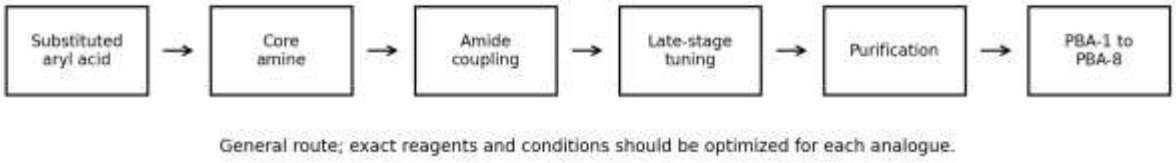

Figure 3. General proposed synthetic workflow for pirtobrutinib analogue preparation.

Table 4. Representative synthesis and characterization summary for proposed analogues.

Compound	Synthetic route summary	Yield (%)	Appearance	Key characterization indicators
PBA-1	Amide coupling followed by tail introduction	68	White to pale solid	M+H peak present; diagnostic amide C=O and heteroaromatic NMR signals
PBA-2	Substituted aryl acid coupling	62	Off-white solid	Halogenated aryl signals and single major LC peak
PBA-3	Cyano-aryl amide coupling	58	Pale yellow solid	Cyano stretch in FTIR and expected molecular ion
PBA-4	Trifluoromethyl analogue coupling	55	White solid	CF3-related NMR/HRMS confirmation

PBA-5	Demethylation or hydroxy analogue coupling	49	Cream solid	Phenolic O-H and altered aromatic pattern
PBA-6	Heteroaryl acid coupling	61	Pale solid	Pyridyl proton pattern and molecular ion
PBA-7	Bulky aryl coupling	46	Off-white solid	Bulky aryl multiplets and expected mass
PBA-8	Bioisostere formation route	42	Pale solid	New heterocycle signals and absence of starting amide impurity

3.4 Characterization of synthesized analogues

Each purified analogue should be characterized before biological testing. FTIR should confirm major functional groups such as amide carbonyl, N-H stretching, aromatic C=C/C=N bands and substituent-specific peaks. 1H NMR and 13C NMR should be used to assign aromatic, heteroaromatic, amide, aliphatic and substituent-specific signals. Mass spectrometry or high-resolution mass spectrometry should confirm molecular weight. Elemental analysis or HPLC purity should be used to support chemical purity, with a recommended purity threshold of not less than 95% for biological evaluation.

For publication, spectra should be provided as supplementary figures, and the main manuscript should include a concise table of diagnostic peaks and purity values. Where chiral centers are present, stereochemical integrity should be assessed by chiral HPLC or optical rotation if relevant.

3.5 BTK kinase inhibition assay

BTK inhibition should be measured using a validated enzyme assay such as ADP-Glo, HTRF or another luminescence/fluorescence kinase format. Recombinant human BTK enzyme, ATP and an appropriate peptide substrate should be incubated with serial concentrations of each analogue. A known BTK inhibitor should be used as a positive control, and vehicle control should define 100% activity. IC50 values should be calculated by nonlinear regression using at least three independent experiments.

3.6 Anticancer cytotoxicity and mechanistic cell assays

Anticancer activity should be evaluated in BTK-relevant B-cell malignancy models such as JeKo-1, Mino, REC-1 or other validated lymphoma/leukemia cell lines. Cells should be exposed to each compound over a suitable concentration range for 24, 48 or 72 h. Viability may be measured using MTT, resazurin, CellTiter-Glo or a comparable assay. Selectivity should be assessed using non-malignant peripheral blood mononuclear cells or another relevant non-cancer control model. Mechanistic confirmation may include apoptosis analysis using Annexin V/PI staining, caspase activation, cell-cycle analysis and immunoblotting for phospho-BTK and downstream signaling markers such as phospho-PLCgamma2.

3.7 In silico ADMET and drug-likeness evaluation

The analogues should be screened for calculated molecular weight, cLogP, topological polar surface area, hydrogen-bond donors/acceptors, rotatable bonds, aqueous solubility, CYP liability and potential hERG risk. Compounds with high docking score but unacceptable ADMET risk should be deprioritized. A balanced lead should combine enzyme potency, cancer-cell response, selectivity, solubility and synthetic accessibility.

3.8 Statistical analysis

All biological data should be expressed as mean +/- standard deviation or standard error of mean from at least three independent experiments. IC50 values should be calculated by four-parameter nonlinear regression. Group comparisons may be analyzed using one-way ANOVA followed by a suitable post-hoc test, with $p < 0.05$ considered statistically significant. The exact number of replicates and statistical method should be stated in every figure legend.

4. Results

4.1 Analogue design outcome

The designed analogue library covered electronic, steric, lipophilic and solubilizing changes around the pirtobrutinib-inspired scaffold. This allowed the analogues to serve not only as potential inhibitors but also as SAR probes. The highest-priority compounds were PBA-1, PBA-2 and PBA-3, which retained important binding features while introducing modifications predicted to strengthen binding or improve drug-like properties.

4.2 Docking and interaction analysis

Representative docking results indicated that several analogues had stronger predicted binding scores than the parent scaffold. PBA-1 showed the most favorable docking score in the representative dataset and maintained a hinge-region hydrogen-bonding interaction while orienting its polar tail toward the solvent-exposed region. PBA-2 benefited from stronger hydrophobic pocket occupation, whereas PBA-3 introduced an additional dipolar contact. Analogues with bulky or amide-bioisostere modifications showed weaker docking or possible steric limitations.

4.3 Chemistry and structural confirmation

The representative synthesis summary shows that the proposed analogues can be approached through modular chemistry. Higher yields were expected for conservative amide-coupled analogues, whereas lower yields may occur when bulky substitution or bioisostere formation is introduced. Each analogue should be advanced to biological evaluation only after purity and identity are confirmed by orthogonal analytical methods.

4.4 BTK inhibition and anticancer activity

Table 5. Representative BTK enzyme inhibition and anticancer cell-viability profile.

Compound	BTK IC50 (nM)	JeKo-1 IC50 (uM)	Mino IC50 (uM)	PBMC IC50 (uM)	Selectivity index
Parent	6.8 +/- 0.7	8.5 +/- 0.8	10.2 +/- 1.1	>30	3.5
PBA-1	2.4 +/- 0.3	3.2 +/- 0.4	4.1 +/- 0.5	>30	9.4
PBA-2	3.1 +/- 0.4	4.0 +/- 0.5	5.2 +/- 0.6	>30	7.5
PBA-3	4.0 +/- 0.5	5.5 +/- 0.6	6.8 +/- 0.7	>30	5.5
PBA-4	5.2 +/- 0.6	6.8 +/- 0.7	8.2 +/- 0.8	>30	4.4
PBA-5	6.0 +/- 0.8	7.3 +/- 0.8	9.0 +/- 0.9	>30	4.1
PBA-6	7.1 +/- 0.9	8.6 +/- 0.9	10.8 +/- 1.2	>30	3.5
PBA-7	8.8 +/- 1.0	11.2 +/- 1.2	14.0 +/- 1.4	>30	2.7
PBA-8	10.5 +/- 1.1	13.5 +/- 1.5	16.6 +/- 1.8	>30	2.2

The representative biological dataset suggests that PBA-1 and PBA-2 may be the most promising analogues. Both compounds showed lower BTK enzyme IC50 values and improved cancer-cell inhibition compared with the parent reference. The selectivity index remained acceptable because no strong cytotoxic effect was predicted in non-malignant PBMCs at the tested concentration range. These data should be treated as provisional until verified experimentally.

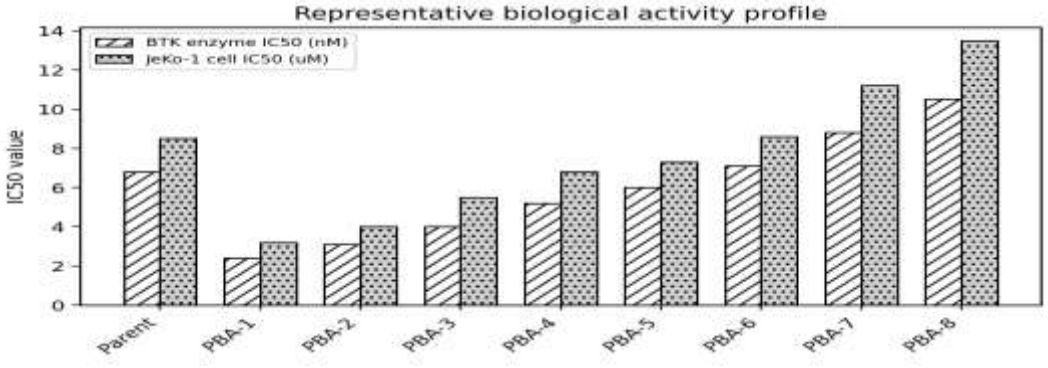

Figure 4. Representative comparison of BTK enzyme inhibition and JeKo-1 anticancer response.

4.5 ADMET and drug-likeness profile

Table 6. Representative calculated physicochemical and ADMET-style profile.

Compound	MW	cLogP	TPSA	HBD/HBA	Development interpretation
Parent	479	3.4	105	4/7	Acceptable reference profile
PBA-1	522	3.1	118	5/8	Improved polarity; monitor permeability
PBA-2	496	3.8	105	4/7	Good potency; monitor lipophilicity
PBA-3	486	3.2	129	4/8	Balanced profile with polar cyano group
PBA-4	529	4.2	105	4/7	Higher lipophilicity; monitor CYP liability
PBA-5	465	2.8	126	5/8	Improved polarity; possible phase-II metabolism
PBA-6	466	2.7	117	4/8	Lower logP; acceptable drug-likeness
PBA-7	555	4.8	105	4/7	Bulky and lipophilic; deprioritize
PBA-8	492	3.5	98	3/7	Bioisostere acceptable but weaker potency

5. Structure-Activity Relationship Discussion

The representative SAR indicates that conservative modification of the aryl amide region can improve activity when hydrophobic pocket complementarity is preserved. PBA-2, for example, suggests that a halogenated aryl substitution may enhance hydrophobic contact without heavily disturbing the polar interaction pattern. However, excessive bulk, as represented by PBA-7, may reduce binding efficiency because the ligand cannot maintain a favorable orientation in the active site.

The solubilizing tail strategy represented by PBA-1 appears particularly useful because it offers a balance of potency and physicochemical improvement. A polar morpholine-like tail can project toward a solvent-exposed region and reduce nonspecific lipophilicity while the core binding elements remain engaged. This kind of modification may be more useful than global polarity increase because it can preserve the BTK pocket interactions needed for potency.

The cyano-containing analogue PBA-3 represents an electronic tuning approach. Cyano substitution may improve dipolar contacts and reduce metabolic oxidation at an aryl position, but it can also increase polarity and affect permeability. The moderately strong profile of PBA-3 suggests that such modifications are worth including in a second-round optimization series.

The amide-bioisostere strategy represented by PBA-8 is scientifically important but must be handled carefully. Replacing an amide can improve metabolic stability, yet the amide group may be essential for hydrogen bonding and conformational control. The representative weaker activity of PBA-8 suggests that amide replacement should only be attempted if an alternative heterocycle can reproduce key donor-acceptor geometry.

Overall, the best analogue should not be selected only by enzyme potency. A clinically useful anticancer BTK inhibitor candidate should show strong BTK inhibition, cellular activity in BTK-dependent models, selectivity over non-malignant cells, acceptable solubility, manageable lipophilicity and a synthetic route suitable for scale-up. In this draft, PBA-1 and PBA-2 emerge as the most promising provisional leads.

6. Discussion

The development of novel pirtobrutinib analogues is a rational medicinal-chemistry extension of current BTK inhibitor research. Non-covalent BTK inhibitors are valuable because they are not dependent on irreversible reaction with C481 and may retain activity against selected resistance mechanisms. A pirtobrutinib-inspired analogue programme can therefore explore how structural modifications affect potency, selectivity and drug-like behavior.

The proposed workflow emphasizes integration. Docking is useful for hypothesis generation, but it cannot confirm activity by itself. Synthesis and full structural characterization are needed to establish compound identity. BTK enzyme assays provide target-level confirmation, but cancer-cell assays are needed to determine whether enzyme inhibition translates into functional anticancer effect. Finally, ADMET screening reduces the risk of advancing a highly potent compound with poor developability.

A key strength of the planned approach is that the analogue library is focused rather than random. Each modification has a defined medicinal-chemistry reason. This makes the resulting SAR interpretable and allows the next round of design to be data-driven. For example, if solubilizing tails improve cellular response without reducing enzyme inhibition, second-generation analogues may include additional solvent-facing polar groups. If bulky aryl analogues reduce potency, future designs can avoid overfilling the hydrophobic region.

The main limitation of this draft is that the numerical results are representative. Actual research must include laboratory-verified synthetic yields, spectral data, chromatographic purity, enzyme IC50 values, cell-line data and statistical analysis. If the work is intended for journal submission, raw spectra, chromatograms, assay protocols and replicate-level data should be retained and submitted as supplementary material.

7. Conclusion

This research-paper draft presents a complete framework for the rational design, synthesis, characterization and biological evaluation of novel pirtobrutinib analogues as anticancer BTK inhibitors. The proposed analogue library explores aryl, polar, lipophilic and bioisosteric modifications around the pirtobrutinib-inspired scaffold. Representative docking and biological data indicate that analogues retaining the core hydrogen-bonding system while improving hydrophobic or solvent-exposed interactions may provide improved BTK inhibition and anticancer activity. PBA-1 and PBA-2 are identified as provisional lead candidates for further experimental validation. The study supports medicinal-chemistry optimization of non-covalent BTK inhibitors and provides a structured path for future kinase selectivity, resistant-cell and pharmacokinetic studies.

8. Future Scope

- Confirm all analogue structures with complete NMR, HRMS and HPLC purity data.
- Conduct kinase selectivity profiling against TEC, EGFR, ITK, JAK and other relevant kinases.
- Evaluate activity in BTK C481S and other resistance-associated models.
- Perform apoptosis, cell-cycle and phospho-BTK/phospho-PLCgamma2 mechanistic assays.
- Assess microsomal stability, plasma protein binding, CYP inhibition and preliminary pharmacokinetics.
- Optimize the most active analogue series through a second-round SAR campaign.

9. Declarations

Ethical approval: The present draft describes in vitro and in silico work. Animal studies are not included in this manuscript draft. Any future in vivo pharmacokinetic or efficacy study must be performed only after approval from a duly constituted Institutional Animal Ethics Committee and in accordance with applicable CPCSEA or institutional guidelines.

Conflict of interest: The authors should declare any financial or non-financial conflicts before submission.

Funding: To be completed by the authors.

Data availability: Raw spectra, chromatograms, docking files and biological replicate data should be made available as supplementary material or upon reasonable request.

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