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Discovery of *Glycyrrhiza glabra* compounds as potent lymphocyte-specific protein tyrosine kinase inhibitors *via in silico* approaches

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Acute lymphoblastic leukaemia (ALL) is a rapidly progressing malignancy of bone marrow and blood. Dysregulated activity of the pre-T-cell receptor-lymphocyte-specific protein tyrosine kinase (LCK) has been linked to enhanced cell proliferation, contributing to T-cell ALL. LCK inhibition with specific drugs has the potential to reverse treatment resistance and provide a therapeutic option for a significant number of T-ALL patients. In this study, 450 compounds from *Glycyrrhiza glabra* (*G. glabra*) were screened against LCK using insilico techniques. The virtual screening and visual inspection of the compounds' interactions with LCK active site residues revealed that 13 compounds exhibited higher binding affinity than the control molecule. The top four compounds—LTS0002748, LTS0007245, LTS0031098, and LTS0014950—were subjected to detailed interaction analysis, demonstrating their interaction with LCK active site residues and sharing multiple interacting residues with the positive control. Furthermore, these compounds possess favorable drug-like properties and minimal toxicity concerns, making them promising candidates for use as LCK inhibitors in leukaemia treatment. However, additional experimental validation is needed to optimize these compounds as potential LCK inhibitors.

Keywords: Acute lymphoblastic leukaemia, Drug-likeness, Natural compounds, T-cell receptor

Leukemia encompasses a broad category of blood malignancies characterized by the abnormal, uncontrolled proliferation of white blood cells[1]. It is the leading cause of cancer-related deaths among men under 40 and women under 20. In 2020, approximately 60, 530 new cases were diagnosed, with an estimated 23, 100 fatalities from the disease[2].

T-cell acute lymphoblastic leukaemia (T-ALL) affects thousands of people each year, with the frequency rising in the United States[3]. It is classified into seven molecular subgroups based on transcription factor activity and T-cell developmental arrest[4,5]. Despite numerous oncogenic drivers, T-ALL cells rely on common pathways, particularly the PI3K/AKT/mTORC1 pathway, which promotes proliferation, stem cell growth, and resistance to therapies such as dexamethasone[6-8]. The activation of this pathway contributes to the significant clinical problem of relapses and refractory disease, with survival rates dropping to 30% in children and less than 10% in adults[3,9]. Therefore, targeting resistant T-ALL cells remain a critical therapeutic priority.

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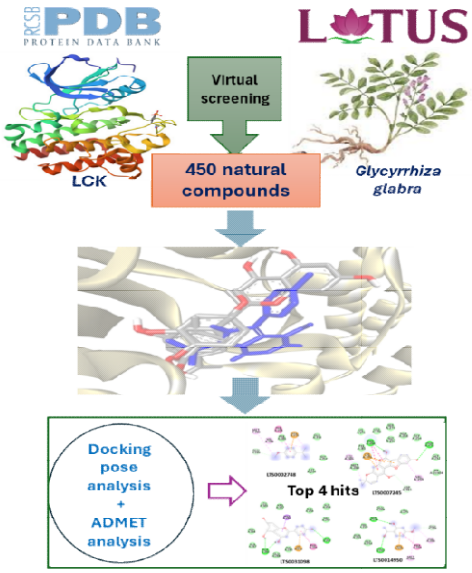
The lymphocyte-specific protein tyrosine kinase (LCK) , a member of the SRC-family kinases, is essential for T-cell activation via T-cell receptor (TCR) signaling and is exclusively expressed in T cells[10]. LCK is also crucial in thymic T-cell progenitors for transmitting proliferative signals from the pre-TCR complex, which is vital for early T-cell development[11]. Dysregulated pre-TCR-LCK activity is associated with increased cell proliferation, contributing to T-ALL, an aggressive hematological malignancy with a poor prognosis due to resistance or recurrence[12]. Currently, T-ALL treatment options are limited, emphasizing the need to identify druggable targets and develop new therapeutic approaches.

It is widely recognized that drug research and development are time-consuming and resource intensive procedures. There is an ongoing effort to leverage computational power to navigate the combined chemical and biological space to expedite drug discovery, development, and optimization. In the biomedical field, computer-aided drug design is employed to speed up and facilitate hit identification and hit-to-lead selection, optimize toxicity profiles, and address safety concerns[13]. *Glycyrrhiza glabra*



Graphical abstract

(*G. glabra*) is a medicinal herb. *G. glabra* and its bioactive components have been shown to have a variety of pharmacological effects, including antimicrobial, antiulcer, anticancer, anti-inflammatory, and antidiabetic properties. *G. glabra* phytochemicals show great promise for developing new herbal medications, and derivatives of these substances are being developed to test their pharmacological properties for future medicinal applications[14,15]. This study utilized biocomputational screening to identify bioactive components of *G. glabra* that interact with the active sites of LCK. Interaction analyses were conducted and compared with the positive control to identify effective natural LCK inhibitors for potential application in leukaemia treatment.

Materials and Methods

Protein preparation

The three-dimensional crystal structure of LCK (PDB ID: 1QPE) was obtained from the Protein Data Bank. The protein structure was prepared using Discovery Studio Visualizer 2020 by removing water molecules, the default ligand, and heteroatoms. The refined protein structure was subsequently saved in PDB format for further docking studies.

Compound retrieval and library preparation from G. glabra

The bioactive compounds of *G. glabra were* sourced from the LOTUS database, one of the largest and most comprehensively annotated resources for natural products[16]. A total of 450 natural products were retrieved in SDF format. These compounds underwent energy minimization using the PyRx tool with the Universal Force Field (UFF) to optimize their geometry. The minimized compounds were then converted into PDBQT format to prepare them for virtual screening (VS) and docking studies.

Virtual screening

Structure-based VS employs computational models of complexes to identify compounds that interact favorably with a biological macromolecule. The recent expansion of commercially available chemical space allows for the search for ligands of therapeutic targets among billions of molecules[17]. Following protein and compound library preparation, the grid box parameters were configured to encompass the protein's active region, with XYZ coordinates of 23.438000, 37.122458, and 84.184917, respectively, and affinity (grid) maps sized at 60 × 60 × 60°. AutoDock Vina was utilized, employing a scoring system to evaluate potential ligand conformations within the target binding pocket. The affinity binding score was calculated in kcal/mol.

Molecular descriptor analysis and ADMET prediction

The molecular descriptors and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) characteristics of the four best-screened compounds were analyzed using the ADMETlab 3.0 web server[18]. This methodology anticipated the pharmacokinetic characteristics and toxicity profiles of the identified compounds, enabling us to evaluate their drug-like properties.

Results

This study used a biocomputational screening methodology to identify bioactive compounds in *G. glabra* that target the active sites of LCK. A total of 450 compounds were obtained from the LOTUS database and subjected to structure basedVS. Comprehensive 2D and 3D molecular interaction analyses were performed, and the results were compared to the positive control, PPT. The goal was to identify potent natural LCK inhibitors for potential use in leukaemia therapy.

The VS and visual analysis of the interactions between the compounds and the active site residues of LCK indicated that 13 compounds demonstrated superior binding affinity compared to the control compound (Table 1) .

This study further investigates the top four identified compounds: LTS0002748, LTS0007245,

LTS0031098, and LTS0014950, focusing on their detailed interaction analysis, molecular descriptor analysis, and ADMET prediction to ascertain their drug-like properties.The binding poses of the top four compounds, along with the control compound, are illustrated in (Fig. 1) .

LTS0002748 interacted with LCK through 9 amino acids residues namely, Glu288, Met280, Val259, Phe256, Phe285, Lys273, Glu258, Gly257, and Gly254 (Fig. 2) . In contrast, LTS0007245 interacted with 15 amino acid residues: Met280, Leu385, Lys273, Phe285, Phe256, Lys276, Leu275, Gly257, Ser274, Glu258, Gly254, Ala253, Gly252, Val259, and Asp382 was found to interact with LTS0007245 (Fig. 2) . LTS0068303 interacted with Glu258, Val259, Gly257, Lys273, Phe256, Phe285, Ile314, Ala284, Glu288, Ala287, Gly384, Arg387, Leu385, and Met280 residues of LCK (Fig. 2) . LTS0031098 interacted with LCK through 14 amino acid residues: Glu288, Ala284, Ala287, Gly384, Leu385, Arg387, Met280, Glu258, Gly254, Val259, Gly257, Phe256, Lys273, and Phe285 (Fig. 2) . Meanwhile, LTS0014950 interacted with 12 amino acid residues: Lys273, Gly257, Gly254, Gln255, Val259, Ser274, Glu258, Leu275, Glu288, Phe285, Phe256, and Met280 (Fig. 2) . Furthermore, the control compound PP2 was found to bind with Val259, Tyr318, Met319, Leu251, Glu317, Gly322, Val301, Thr316, Glu288, Ile314, Lys273, Met292, Ala381, Asp382, Leu371, and Ala271 residues of LCK (Fig. 2) .

Table 1 — Top screened compounds from *G. glabra* compared to the control compound based on binding affinity

S. No.	Ligand	Binding affinity (kcal/mol)
1.	LTS0007245	-7.1
2.	LTS0002748	-6.9
3.	LTS0031098	-6.8
4.	LTS0014950	-6.7
5.	LTS0021358	-6.7
6.	LTS0248198	-6.7
7.	LTS0251224	-6.5
8.	LTS0135332	-6.4
9.	LTS0015369	-6.4
10.	LTS0067434	-6.3
11.	LTS0092525	-6.3
12.	LTS0110109	-6.3
13.	LTS0216892	-6.3
14.	PP2	-6.2

The LOTUS database facilitated the assessment of molecular descriptors, encompassing NP-likeness scores, Lipinski's Rule of Five, and additional relevant criteria (Table 2) . Additionally, toxicity assessments of the four leading compounds were conducted using the ADMETlab 3.0 web server. The radar plots indicate that these compounds exhibit favorable drug-like properties and minimal toxicity concerns, making them suitable candidates for subsequent drug development (Fig. 3) .

Figure 3 displays radar plots that encapsulate the ADMET predictions for the four leading compounds, generated by the ADMETlab 3.0 web server. Each radar plot depicts the molecular characteristics of a

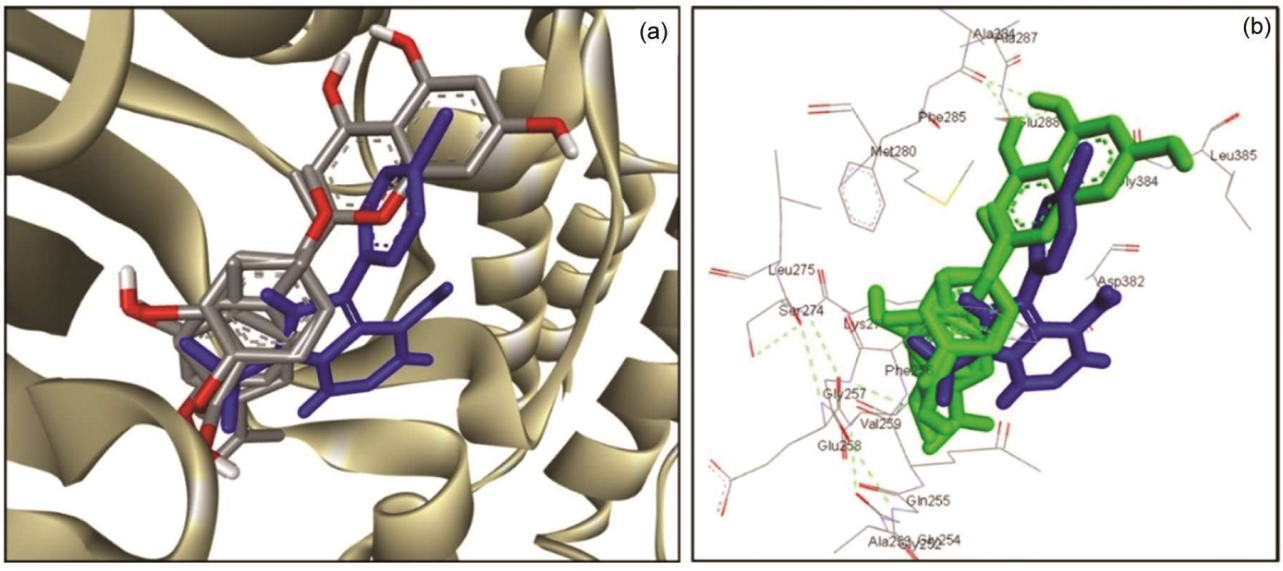


Fig. 1 — Binding poses of the top four compounds and the control compound (Blue) . (a) Binding poses of the compounds within the active pocket of LCK; and (b) 3D interactions of the compounds and the control (blue) with the active site residues of LCK

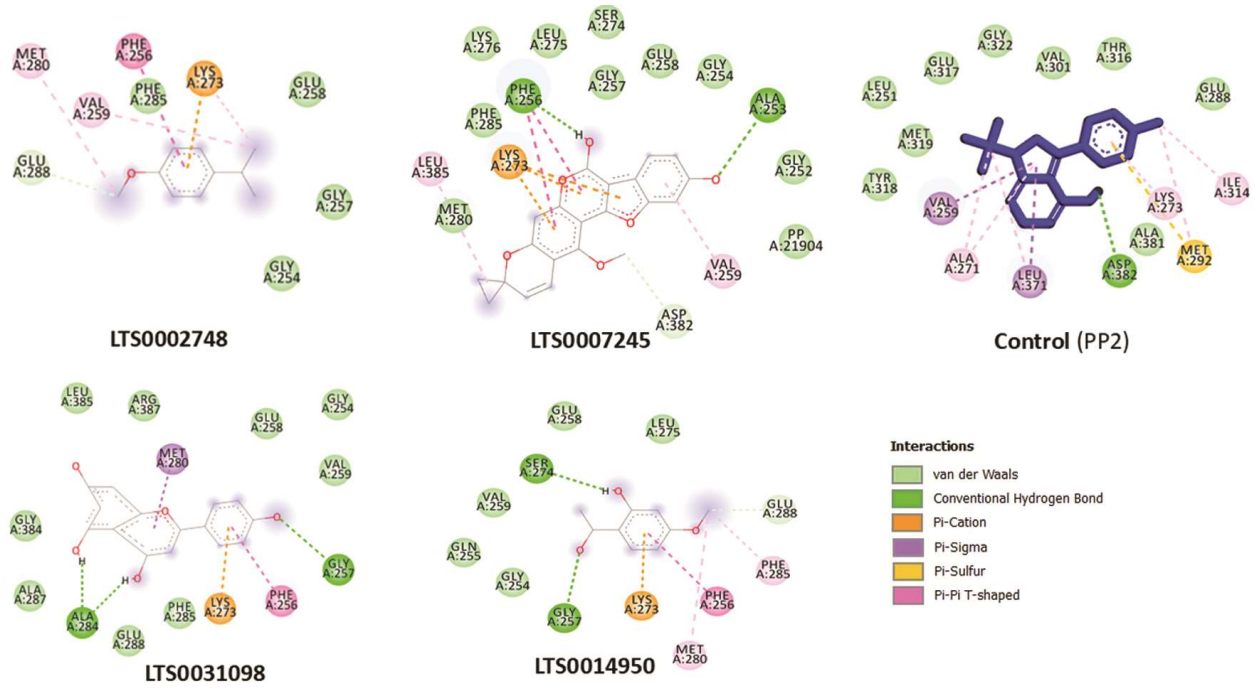


Fig. 2 — 2D interactions of the top four compounds and the control compound with the active site residues of LCK. The interaction types are represented by different colors'

Table 2 — Molecular descriptors of the selected top 4 compounds

Molecular Descriptors	LTS0014950	LTS0031098	LTS0002748	LTS0002748
NP-likeness score	1.04	1.02	1	1
Alogp	1.29	2.3	2.87	4.49
Alogp2	1.65	5.28	8.23	20.12
Apol	24.9139	38.4115	31.7379	53.7743
Bpol	13.8061	15.9925	23.7801	28.2997
Eccentric Connectivity Index Descriptor	122	338	113	543
Fmf Descriptor	0.5	0.8	0.5455	0.7778
Fsp3	0.2222	0.1333	1	0.2857
Fragment Complexity Descriptor	352.03	776.05	851.01	1699.06
Petitjean Number	0.4286	0.5	0.4286	0.5
Lipinski's Rule of 5 Failures	0	0	0	0
Wiener Path Number	197	788	162	1631
Xlogp	1.837	2.029	3.433	4.554
Zagreb Index	56	108	50	160
TopoPSA	46.53	86.99	9.23	82.04

compound in relation to established drug-likeness and toxicity parameters.

The green shaded area denotes the lower threshold for acceptable drug-likeness properties, while the blue region delineates the upper limits. The yellow line represents the anticipated characteristics of each compound. The results indicate that all four compounds fall within acceptable ranges for essential pharmacokinetic and toxicological parameters, withfavorable drug-likeness profiles. The compounds demonstrate no substantialbreaches of drug-like property thresholds, affirming their appropriateness as prospective therapeutic agents for further advancement (Fig. 3) .

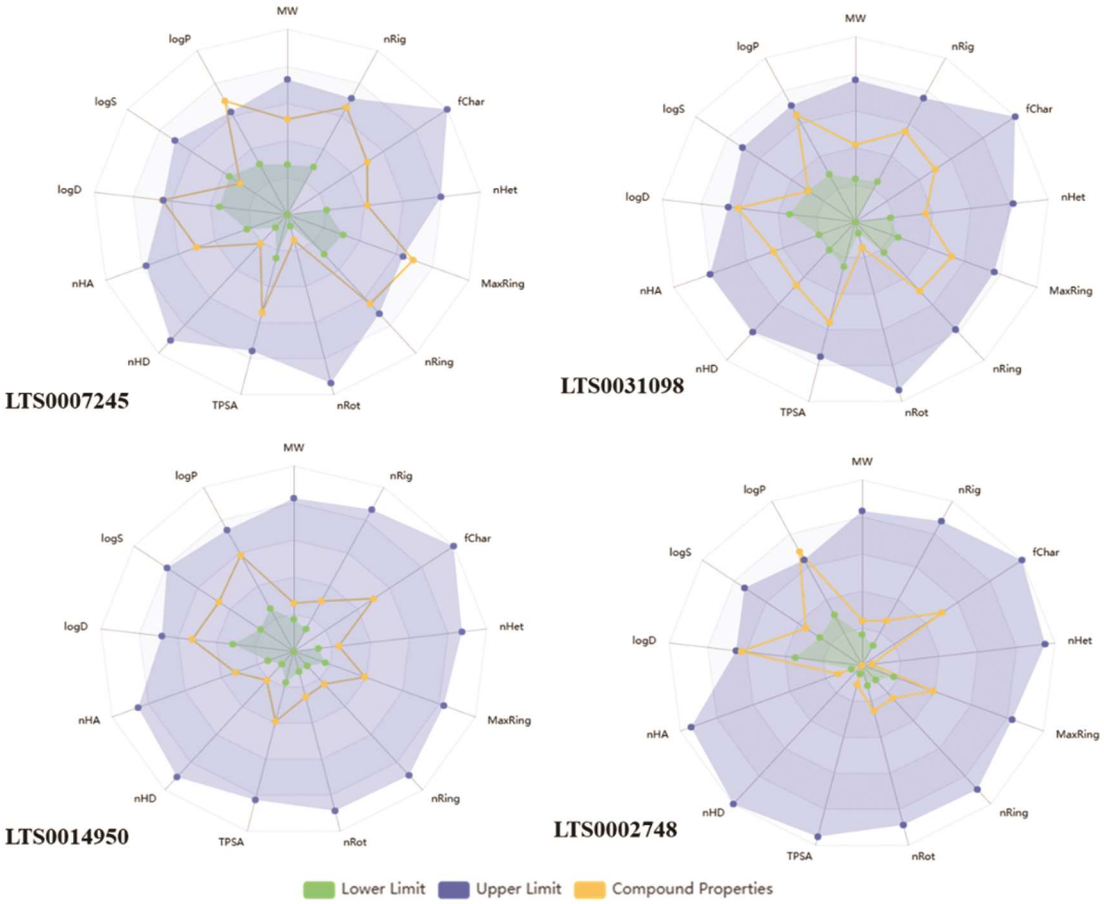


Fig. 3 — Radar plots of ADMET properties for the top four compounds predicted using the ADMETLAB 3.0 web server. The radar plots illustrate the physicochemical and drug-likeness properties of four candidate compounds compared against standard acceptable ranges. Each plot compares key molecular descriptors—such as molecular weight, LogP, hydrogen bond donors/acceptors, and TPSA—using a yellow line representing the compound's profile, enclosed within green (lower limit) and blue (upper limit) boundaries. The closer the compound's properties fall within this acceptable range, the greater its potential as a drug-like candidate. The visual data suggests that while all four compounds display favorable characteristics, some show better alignment with optimal parameters than others, highlighting their suitability for further development

Discussion

Acute leukaemia encompasses a wide range of haematological cancers that affect both children and adults. These tumours often require prolonged treatment regimens, which are frequently accompanied by considerable side effects and consequences[19]. Unlike solid tumors, which usually require genetic mutations and significant cellular reprogramming to enable metastatic progression, leukemic cells exhibit a high propensity for migration and invasion. Malignant leukocytes retain the motility and circulatory survival characteristics of their benign counterparts while demonstrating uncontrolled proliferation capacity. Consequently, while leukemias are not conventionally categorized as metastatic diseases, they exemplify efficient metastatic behaviour. This trait underscores their aggressive nature and the significant challenges they pose in therapy[20]. This study screened *G. glabra* compounds against LCK to identify potential natural LCK inhibitors for leukaemia treatment. The VS revealed that 13 compounds had higher binding affinity than the control compound. Among them, the top four compounds— LTS0002748, LTS0007245, LTS0031098, and LTS0014950 were studied in detail for their interaction analysis and drug-like properties.

PP2, a potent Src family-specific protein tyrosine kinase inhibitor[21], was used as a positive control in this investigation. Val259, Tyr318, Met319, Leu251, Glu317, Gly322, Val301, Thr316, Glu288, Ile314, Lys273, Met292, Ala381, Asp382, Leu371, and Ala271 residues of LCK were found to bind with PP2.

In addition, the residues Glu288, Met292, Val301, Ala381, Asp382, Val259, Leu251, Gly252, Asp326, Ser323, Gly322, Asn321, Glu320, Met319, Tyr318, Glu317, Leu371, Thr316, Ala271, Ile314, Val272, and Lys273 have been shown to be important in binding with LCK[22]. Interestingly, the top four compounds— LTS0002748, LTS0007245, LTS0031098, and LTS0014950 also bind to the majority of these LCK residues.

In docking studies, a lower binding affinity value between the ligand-protein complex indicates that the ligand binds strongly to the target protein and has a lower dissociation rate[23-26]. Notably, the compounds — LTS0002748, LTS0007245, LTS0031098, and LTS0014950 exhibited higher negative binding affinity values than the positive control PP2, indicating strong binding with LCK.

Plants have long been used as folk herbal medicines to treat various diseases, and their phytochemicals have influenced the design, discovery, and development of novel medications. The demand for plant-based medicines, health products, pharmaceuticals, and nutritional supplements is rapidly increasing. *G. glabra* Linn., a commonly used herb in the traditional Ayurvedic system, possesses both medicinal and flavoring properties. The chemical constituents of *G. glabra* suggest its potential as a "lead compound" for the development of innovative medicinal drugs. Research has demonstrated that *G. glabra* and its bioactive components exhibit a wide range of biological activities, including antibacterial, antioxidant, antispasmodic, anti-inflammatory, antihyperglycemic, neuroprotective, antiviral, antihepatotoxic, and anticancer effects[27]. Interestingly, in this study, *G. glabra* compounds have been shown to bind strongly to LCK and can be used as anti-leukaemia agents; further research may confirm that these compounds are potent LCK inhibitors.

It is worth noting that the binding energy values obtained do not reflect the binding efficacy of the compounds with the LCK protein. Further experimental studies are needed to optimize these compounds as potential LCK inhibitors.

Conclusion

Leukaemia is a broad classification of blood cancers. Dysregulated pre-TCR-LCK activity is associated with enhanced cell proliferation, contributing to T-ALL. This study screened *G. glabra* compounds against LCK. The top four compounds LTS0002748, LTS0007245, LTS0031098, and LTS0014950 were thoroughly examined for interaction analysis, revealing interactions with LCK active-site residues. Furthermore, these compounds exhibit favorable drug-like properties, making them promising candidates for LCK inhibition in future drug development. However, additional experimental validation is required to optimize these compounds as potential LCK inhibitors.

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Conflicts of interest

All authors declare no conflicts of interest.

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