

Design and synthesis of oxadiazole and indole-based allosteric cyclin dependent kinase 2 inhibitor for non-toxic ovarian cancer chemotherapy

Tahreem Liaqat¹, Hira Khalid^{1*}, Zainab Shahzad¹, Rashid Hussain¹, Syed Adnan Ali², Farina Hanif², Lubna Khan² and Nazia Ahmed²

¹Department of Chemistry, Forman Christian College University, Lahore-54600, Pakistan.

²Department of Pharmacology & Pharmaceutical Chemistry, Faculty of Pharmacy, Universiti Teknologi MARA Cawangan Selangor Kampus Puncak Alam, Selangor-42300, Malaysia

²Department of Biochemistry, Dow International Medical College, Dow University of Health Sciences, Ojha campus. Karachi Pakistan

E-mail: tehreemliaqat99@gmail.com, hirakhalid@fcccollege.edu.pk

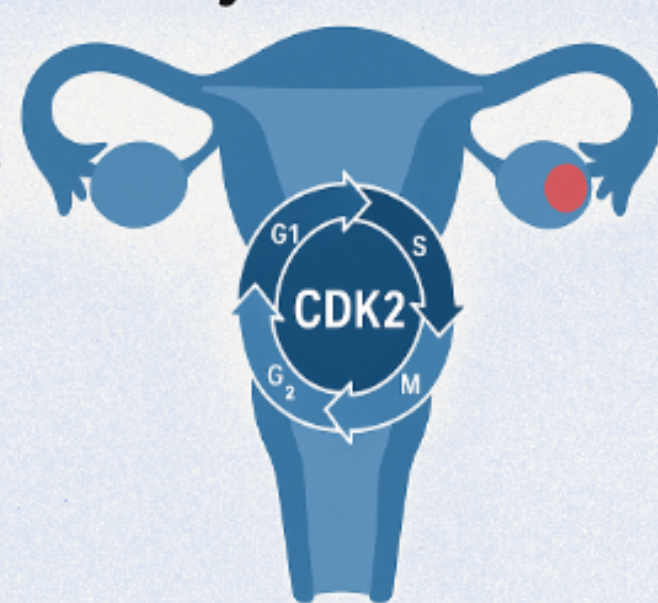
Abstract

Ovarian cancer is the most lethal gynecologic malignancy, driven in part by CDK2 overexpression that disrupts cell cycle control. Targeting CDK2 through selective inhibitors offers a promising therapeutic strategy. In this study, indole- and oxadiazole-based compounds were synthesized, characterized, and evaluated as allosteric CDK2 inhibitors. Molecular docking revealed strong binding affinities, particularly for AO-ZS-02 (–9.8 kcal/mol). Biological testing on ovarian cancer cell lines confirmed dose-dependent growth inhibition, with AO-ZS-02 showing the greatest potency. These findings highlight the potential of heterocyclic scaffolds as lead structures for developing selective, less toxic therapies against ovarian cancer.

Introduction

Ovarian cancer causes highest gynecologic mortality

CDK2 overexpression dysregulates cell cycle, making it a prime therapeutic target.



TOTALS 2022-2050 ⁶	INCIDENCE	MORTALITY
Africa	1,192,000	855,000
Asia	6,601,000	4,342,000
Europe	2,140,000	1,495,000
Latin America & Caribbean	919,000	639,000
North America	843,000	571,000
Oceania	101,000	69,000
Total	11,796,000	7,971,000

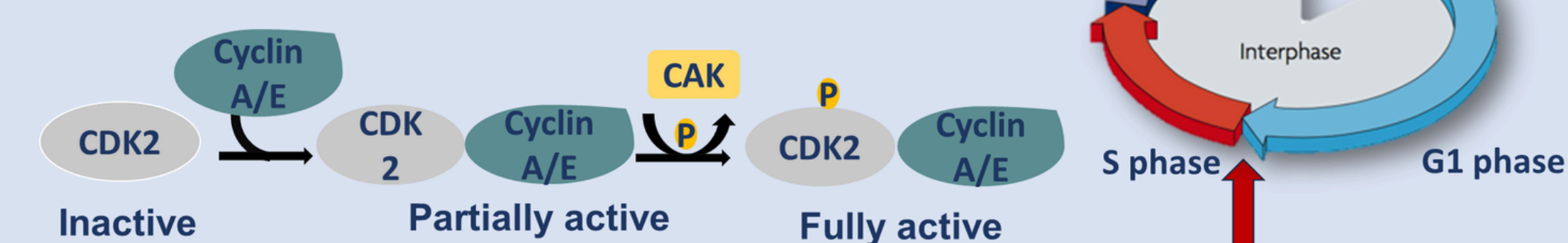
Cyclin-dependent Kinase 2

Serine/threonine protein kinases.

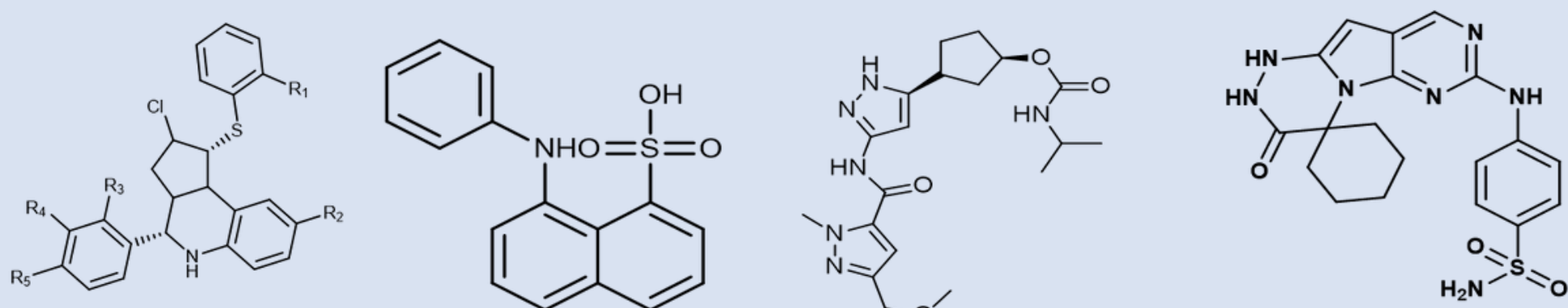
Regulate cell cycle and transcription modulations.

➤ Overexpression of CDK2 ➤ Proliferative diseases, such as cancer

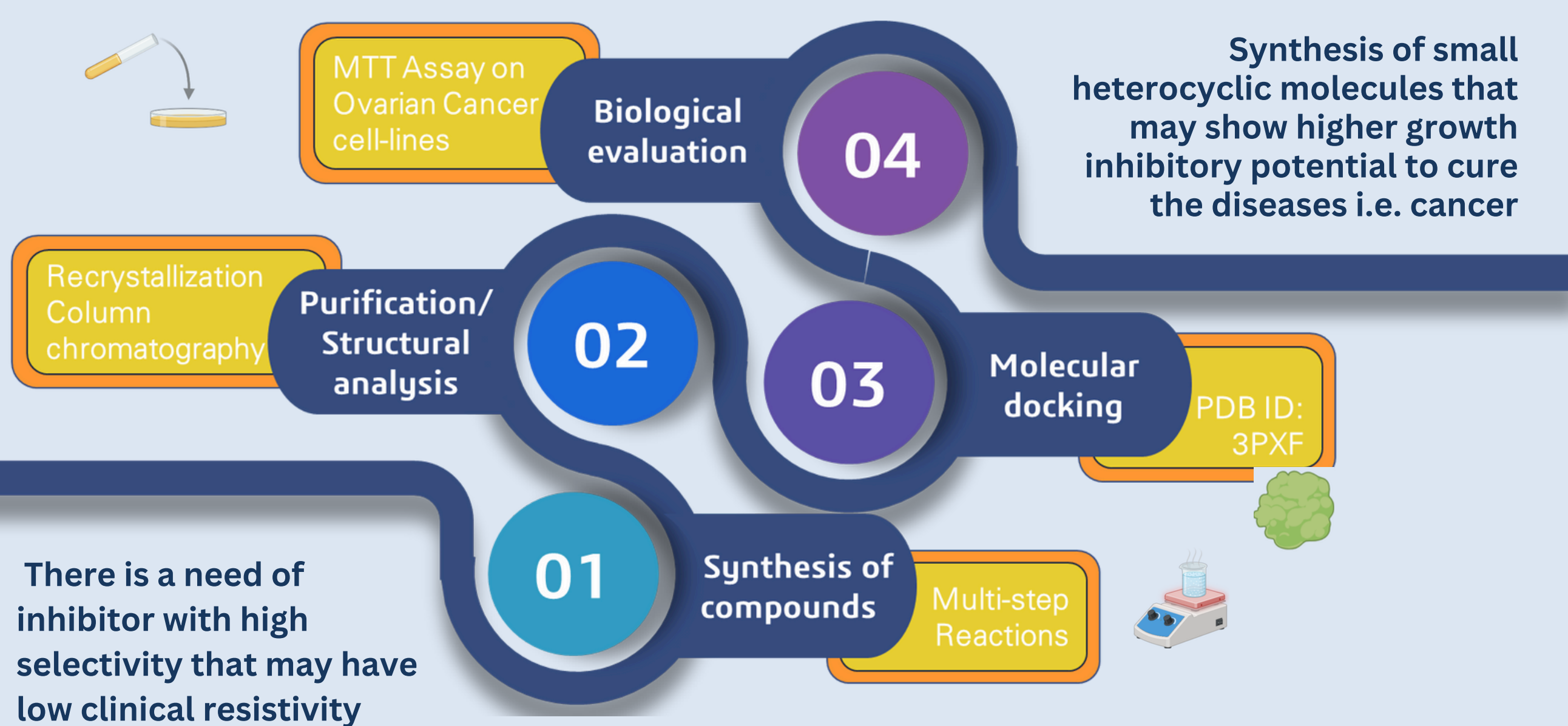
➤ Ovarian Cancer ➤ 6.4% overexpression of CDK2



CDK2 Inhibitors in available in market

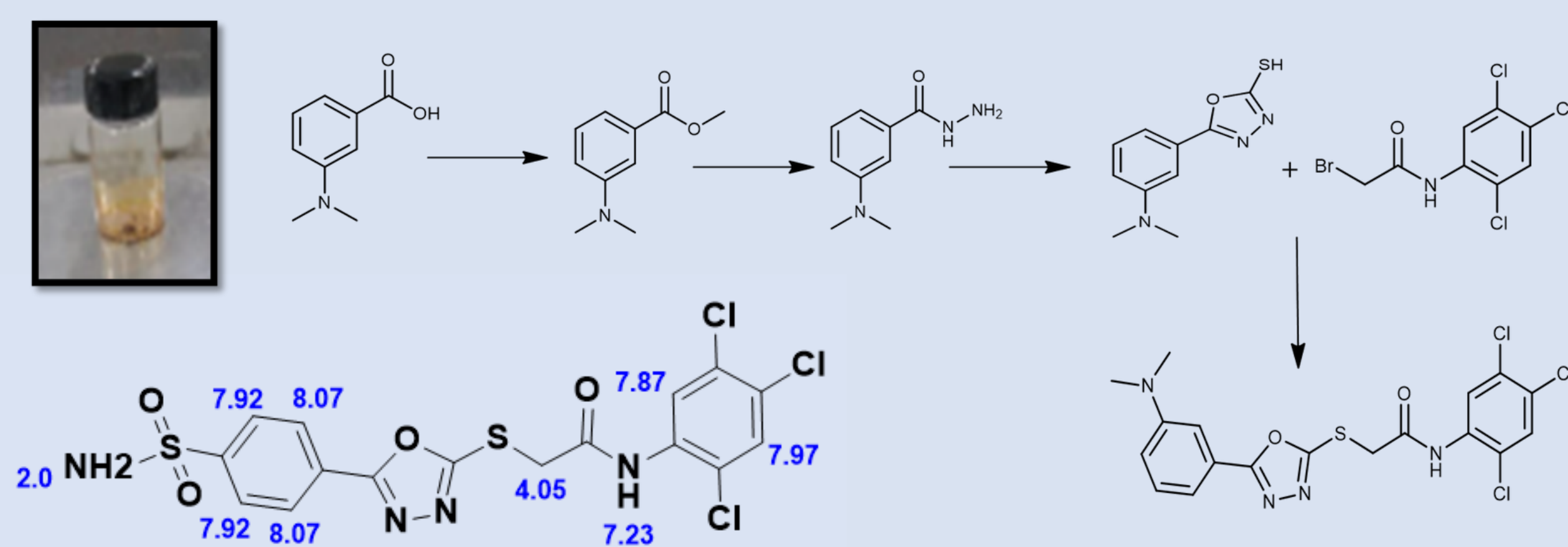


Objective



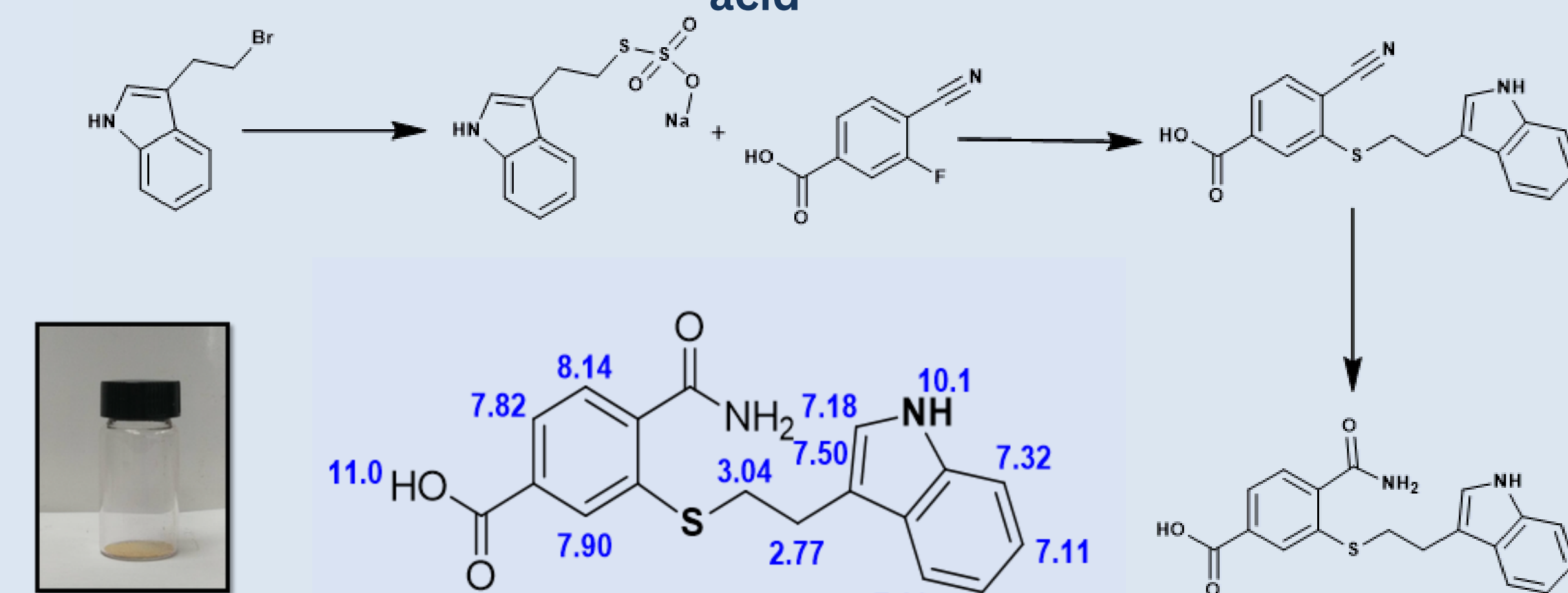
Methodology

Scheme1: Synthesis of 2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(2,4,5-trichlorophenyl)acetamide



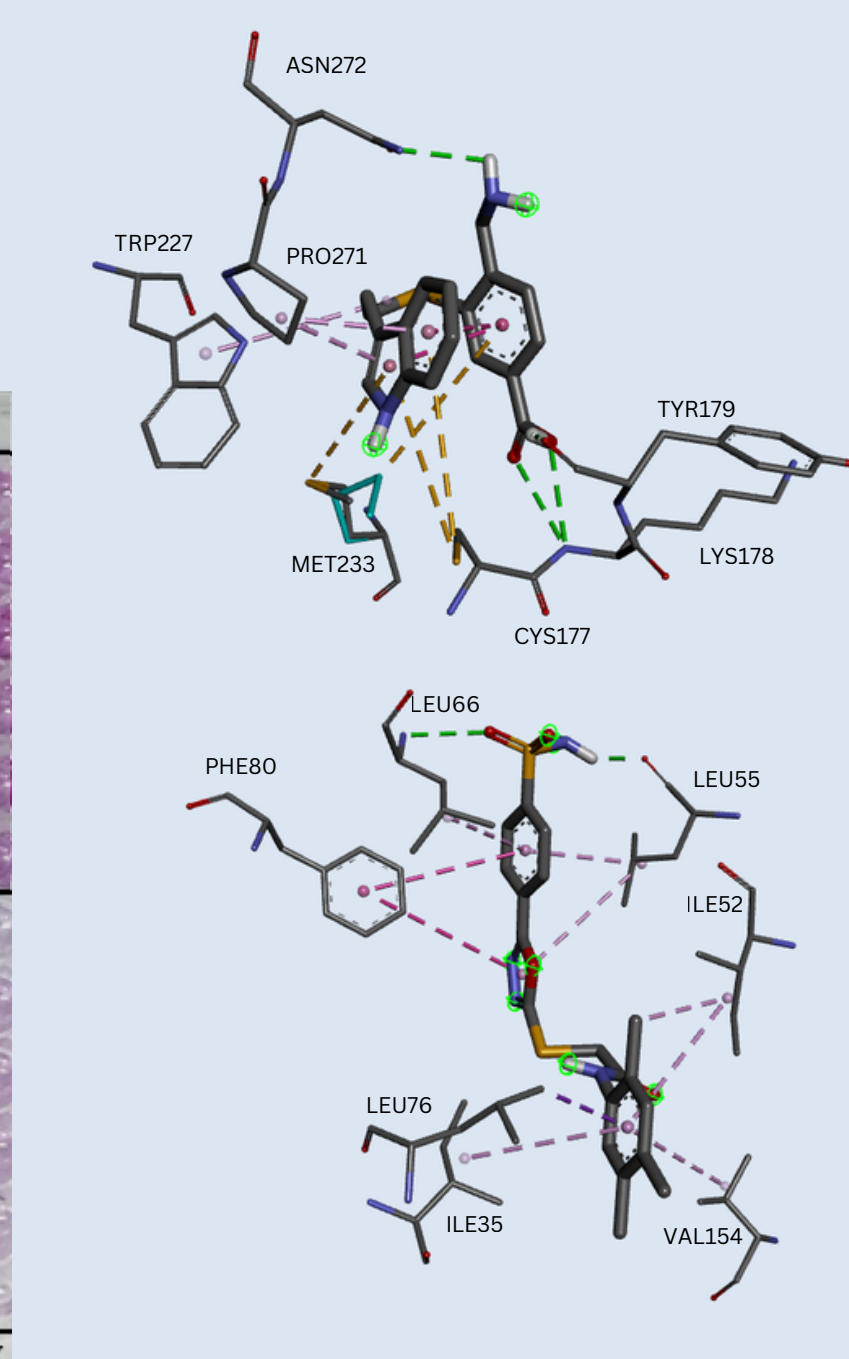
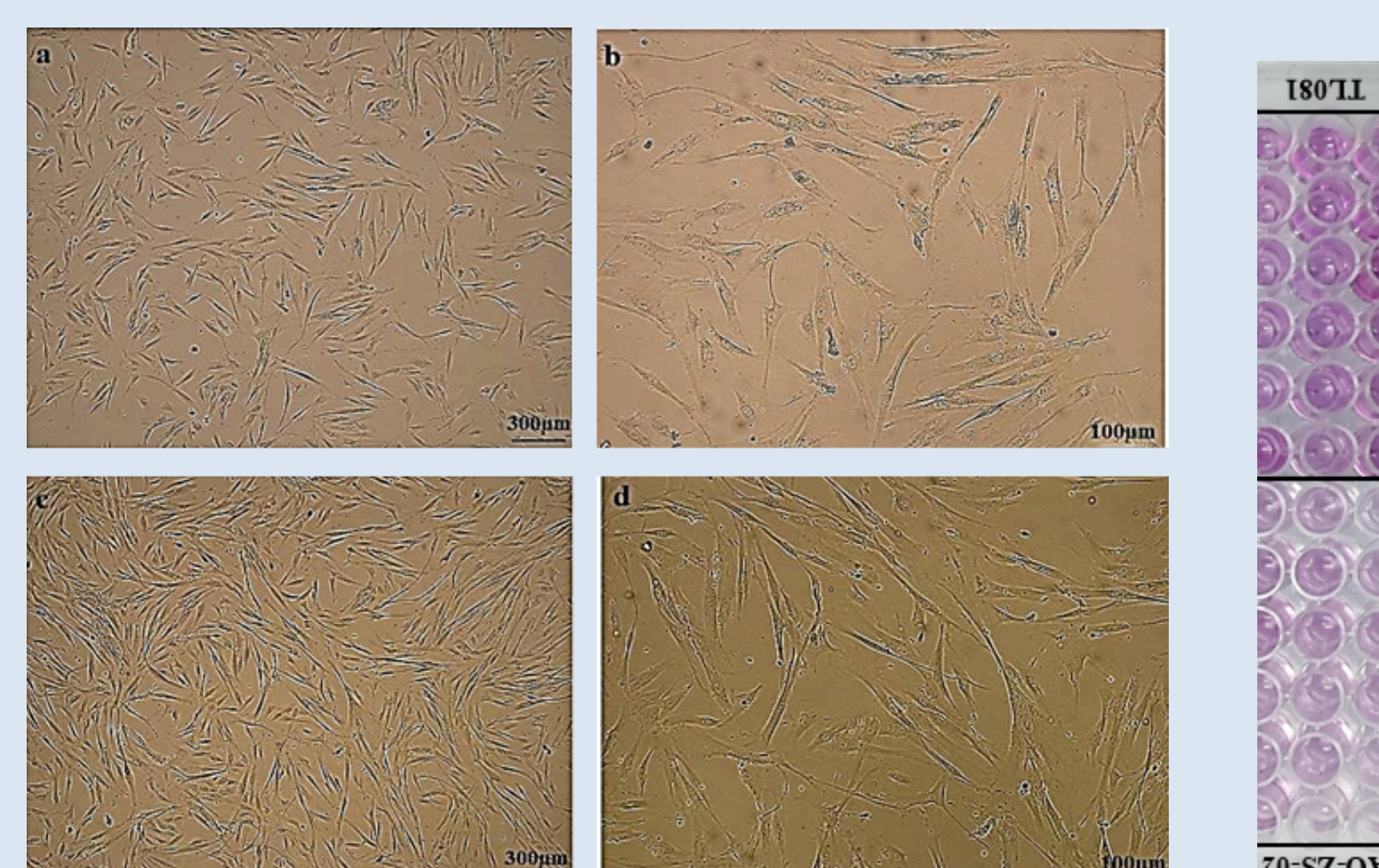
Methodology

Scheme2: Synthesis of 3-((2-(1H-indol-3-yl)ethyl)thio) -4-carbamoylbenzoic acid



In this study, molecular docking was performed to evaluate the binding affinities of compounds against CDK2 using PDB ID: 3PXF.

MTT Assay of synthesized compounds



Results/Conclusion

- The compounds were successfully synthesized, characterized, and biologically evaluated for growth inhibition.
- AO_ZS_02 (oxadiazole-based) exhibited the highest growth inhibition.
- TL081 (indole-based) showed moderate growth inhibition at a moderate concentration.
- The results highlight their potential as therapeutic growth inhibitors, warranting further mechanistic studies.

