

# Insilico Evaluation and ADMET Profiling of Thiophene Based Chalcones as Potential Anticancer Agents

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## ABSTRACT

Aim of the current project's objective was to develop novel thiophene based chalcone derivatives as potential cyclin dependent kinase (CDK) inhibitors, assess binding affinity by molecular docking studies, predict pharmacokinetic and toxicity profile based on SwissADME, pkCSM and ProTox. Methods of Novel derivatives of chalcone were designed. Auto Dock Vina in PyRx was used to conduct molecular docking investigations and insilico evaluation was performed using Swiss ADME, pkCSM, PASS and ProTox. was performed using standard procedures. Results of Fifteen thiophene-based chalcone derivatives (ATP1-ATP15) were successfully designed. Molecular docking demonstrated favourable binding affinities, with ATP1 exhibits a higher docking score (-8.5 kcal/mol). All designed compounds obey Lipinski's rule of five & showed desirable ADMET profiles. In Conclusion the designed thiophene-based chalcones demonstrated promising molecular interactions, pharmacokinetic properties, and significant biological activities, indicating their potential as lead compounds for the development of innovative CDK-targeting anticancer drugs.

**Keywords:** Thiophene chalcones; Cyclin-dependent kinase; Molecular docking; ADME prediction; Anticancer activity; Biological evaluation; Drug discovery.

## 1. INTRODUCTION

Cancer is a kind of tumour that can spread from its original organ to other parts of the body and manifests as aberrant cell proliferation. cancer acquires a variety of malignant characteristics that enable it to penetrate or spread through genetic and epigenetic alterations that disrupt vital cellular functions like DNA degradation and repair, proliferative regulation, and immune destruction avoidance.[1] Cancer cells cause tumours to grow and eventually spread as metastases. Cancer cells seemed to be the source of tumours, or at least to reside within them.[2] The accumulation of consecutive changes to multiple genes, including those generating microRNAs (miRNAs), is a complex multistep process that causes cancer.[3]

CDKs are essential regulators of cell cycle progression. As a result, CDK2 has gained popularity as a molecular target for anticancer medication development. Previously established CDK2 inhibitors, including purine-, pyrimidine-, and other heterocyclic scaffolds, have provided important structural insights for the development of novel CDK2-targeting agents. Examples include Dinaciclib, Seliciclib.

This emphasizes on sulphur-containing heterocyclic, thiophene-substituted chalcone derivatives as these candidates share structural

similarities with active compounds in order to create novel, powerful lead molecules for drug design.[4] Because the thiophene scaffold's core has a variety of biological properties that enable them to operate as anticancer, antibacterial, antifungal and antitubercular agents. It is one of the privileged structures in drug discovery.[5]

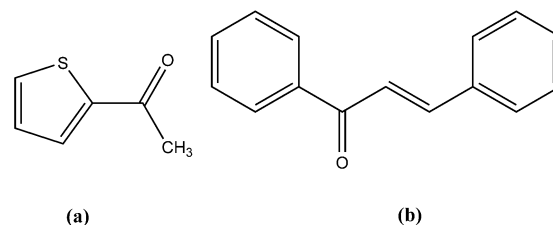


**Figure 1: Chemical structure of (a) Thiophene (b) Chalcone nucleus**

Chalcones are a prominent class of  $\alpha$ ,  $\beta$ -unsaturated ketones noted for the diverse range of pharmacological activities. They are known for their diverse pharmacological activities, have shown promising anticancer potential due to their simple structure and ease of modification.[6] In chalcone-thiophene conjugates, the unsaturated carbonyl (enone) system, specifically its carbon-carbon double bond ( $C=C$ ) and adjacent carbonyl ( $C=O$ ) group, serves as the vital pharmacophore for anticancer binding. The connection point where the thiophene ring attaches directly to the  $\beta$ -carbon of the enone moiety yields optimal target interaction and cytotoxicity.[7]

Although several studies have reported the anticancer potential of chalcone derivatives, thiophene-containing compounds, and various CDK inhibitors, limited information is available on thiophene-based chalcones specifically designed and evaluated as potential CDK2 inhibitors. Furthermore, systematic studies combining molecular docking with ADMET profiling of such compounds are relatively limited. Therefore, further investigation of thiophene-based chalcone derivatives as potential CDK2 inhibitors is warranted.

## 2. MATERIALS AND METHODS

### 2.1. In silico screening, selection of candidate molecule and ADMET prediction

The in-silico investigations were used to assess the compound's drug likeness. This included calculating its bioactivity score, assessing its physicochemical and ADMET characteristics using Lipinski's Rule of Five and using molecular docking to identify the most promising molecules with the intended orientation. Key molecular characteristics necessary for the drug's pharmacokinetics were validated by Lipinski's Rule of Five, mostly with Swiss ADME.

**Lipinski rule of 5:** Lipinski's rule of five was evaluated by an online tool. The PDB files of the ligands were uploaded to the platform, and the analysis was performed by submitting the structures. The results obtained were employed to evaluate the drug likeness of the compounds.

**Pro tox 3.0:** Toxicity prediction was performed using the ProTox 3.0 server. The chemical structures of the ligands were outlined and submitted to the platform for toxicity analysis. The results, including LD<sub>50</sub> values and toxicity classification, were obtained and used to assess the safety parameters of the compounds.

**Swiss ADME:** ADME properties were examined by the Swiss ADME online tool. The chemical structures of the ligands were drawn and converted into SMILES format, which were then submitted for analysis. The results obtained were used to examine the pharmacokinetic characteristics and drug-likeness of the compounds.

### 2.2. Docking methodology

Molecular docking experiments were performed using PyRx 0.8 integrated with the AutoDock Vina docking engine. [8,9] Visualization and analysis of protein-ligand interactions were carried out using BIOVIA Discovery Studio. These software tools were used to assess the binding strength and interaction patterns of the designed ligands with the target protein. Cyclin-dependent kinase 2 (CDK2) was chosen as the biological target due to its well-established role in regulating cell-cycle progression and its significance as a therapeutic target for the development of anticancer drugs. [10] For antiproliferative study, an X-ray crystal structure of human CDK2, denoted by PDB ID 2FVD, was obtained from the protein data bank in order to facilitate further computational investigations. The selection criteria for the protein included the resolution, deposition year, experimental technique, organism and ligand details, as shown in table 1. Co-crystallized ligand was used as a structural reference to locate the ATP-binding pocket and confirm the docking procedure. For the comparative docking analysis, 5-fluorouracil served as the reference compound.

BIOVIA Discovery Studio was utilized to prepare the protein structure. In order to prepare the protein, the co-crystallized ligand, unnecessary heteroatoms and solvent molecules were eliminated. Hydrogen atoms were then added and structural optimization was carried out to obtain a suitable docking model.

## 3. RESULTS

### 3.1 Drug-Likness Properties and Lipinski's Rule of Five Analysis

Lipinski's Rule of Five was used to examine the physicochemical characteristics and drug-likeness of the produced compounds (ATP1–ATP15). Table 3 provides a summary of the findings.

Every synthetic molecule (ATP1–ATP15) showed no breaches of the Lipinski rule, suggesting good drug-like characteristics. The compounds molecular weights fell within the widely recognized range of 500 g/mol, ranging from 228.31 to 340.18 g/mol. Moderate lipophilicity was indicated by the computed Log P values, which varied from 2.77 to 4.81. ATP13

showed more lipophilicity (Log P = 4.81), but it was still below the well-recognized Lipinski threshold of 5.0. All of the HBD and HBA readings, which varied from 0 to 1 and 1 to 3, were well within the suggested ranges of no more than 5 HBD and 10 HBA, respectively.

### 3.2 In Silico ADME Evaluation

Using in silico ADME prediction, the pharmacokinetic and absorption-related characteristics of the produced drugs (ATP1–ATP15) were assessed. Caco-2 permeability, P-glycoprotein (P-gp) inhibition and substrate potential, human intestinal absorption (HIA), permeability, volume of distribution at steady state (VDss), blood brain barrier (BBB), percent unbound (Fu), and clearance were among the metrics evaluated. Table 4.1 provides a summary of the anticipated outcomes.

The drugs exhibited generally good intestinal permeability, with Caco-2 permeability values ranging from 1.192 to 1.861 log Papp. All substances had consistently high intestinal absorption potential, as indicated by the anticipated HIA values, which varied from 91.109% to 97.017%. The log BB value for the standard compound was -0.432. The range of the expected VDss values was 0.121 to 0.681 log L/kg. Each compound had a different fraction unbound (Fu), with generally low free drug fractions. Fu was highest for ATP5 (0.176), followed by ATP15 (0.120) and ATP4 (0.049). The predicted clearance values ranged from -0.293 to 0.202 log mL/min/kg. ATP6 showed the highest predicted clearance (0.202), whereas ATP12 exhibited the lowest value (-0.293). Overall, the designed ATP derivatives demonstrated favourable predicted intestinal absorption and permeability profiles.

In silico prediction was used to assess the designed compounds' (ATP1–ATP15) ability to inhibit key cytochrome P450 (CYP450) isoenzymes.

It was predicted that all of the substances (ATP1–ATP15) would inhibit CYP1A2, suggesting a possible interaction with this metabolic pathway. Similarly, CYP2C19 and CYP2C9 were anticipated to be inhibited by ATP1–ATP14, whereas CYP2C9 was not predicted to be inhibited by ATP15. Predicted inhibitory activity

against CYP2D6 was not demonstrated by any of the produced compounds, indicating a relatively low probability of interaction with this specific metabolic enzyme.

### 3.3 Physicochemical Properties

The table 5 displays the physicochemical characteristics of the produced molecules ATP1–ATP15. The compounds' molecular weights varied between 240.32 and 257.35 g/mol. The molar volume (MV) varied from  $191.1 \pm 3.0$  to  $217.2 \pm 3.0$  cm<sup>3</sup>, while the molar refractivity (MR) ranged from  $74.81 \pm 0.3$  to  $79.80 \pm 0.3$  cm<sup>3</sup>. The compounds ranged in density from  $1.166 \pm 0.06$  to  $1.356 \pm 0.06$  g/cm<sup>3</sup>.

### 3.4. Toxicological Profiles

Characterized by LD50 values between 1000 to 3000 mg/kg, the toxicological profile of ATP1–ATP15 compounds predicted by ProTox-3.0 showed that most compounds were classed under toxicity category 4, whereas ATP3, ATP6, and ATP14 were placed in category 5, indicating somewhat lower acute toxicity. A number of molecules, including ATP3, ATP4, ATP6, ATP14, and ATP15, were projected to be harmful according to the hepatotoxicity projections, while the rest compounds were predicted to be non-toxic. ATP2, ATP3, ATP6, ATP10, and ATP14 were projected to be carcinogenic, whereas the remaining compounds displayed profiles that were not carcinogenic.

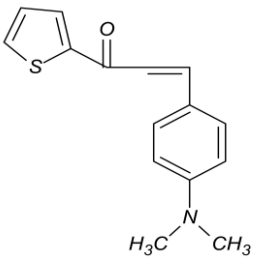
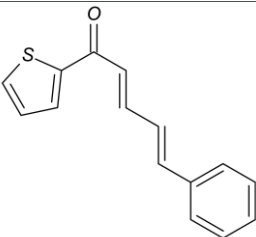
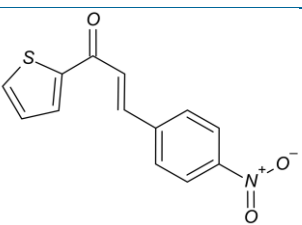
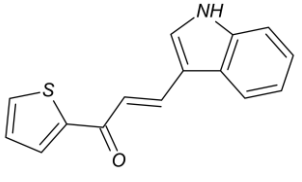
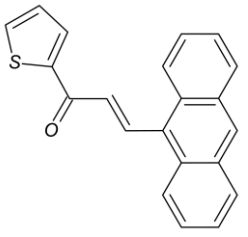
### 3.5 Molecular Docking

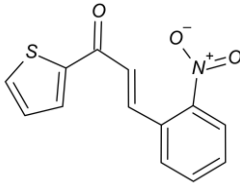
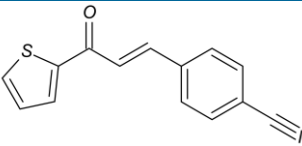
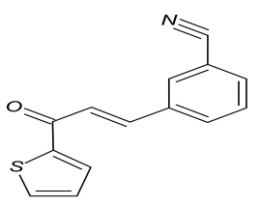
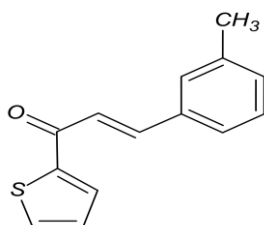
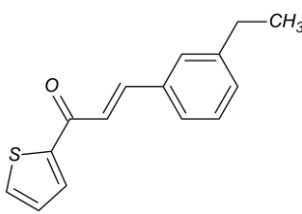
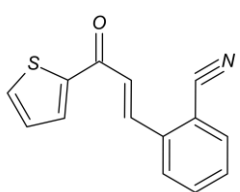
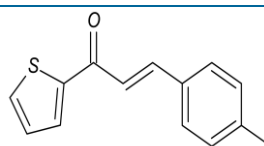
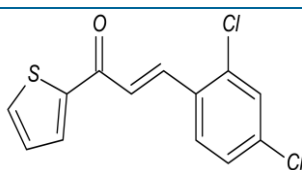
The full set of designed compounds series showed numerous non-covalent contacts with the corresponding target protein binding sites, according to the 2D docking interaction analysis of ATP1–ATP15. In addition to  $\pi$ -related interactions like  $\pi$ - $\sigma$  and  $\pi$ -alkyl contacts, ATP1 mostly displayed van der Waals interactions with a number of amino acid residues, suggesting that the ligand was well accommodated in the binding pocket

**Table 1: Protein parameters (PDB ID: 2FVD)**

| PDB ID | Organism     | Year of deposition | resolution | Experimental method | Unique ligands |
|--------|--------------|--------------------|------------|---------------------|----------------|
| 2FVD   | Homo sapiens | 2006               | 1.85 Å     | X-ray diffraction   | LIA            |

Table 2: Structures, SMILES and docking scores of the designed compounds

| Compound code | Smiles                                               | Structure                                                                            | Binding energy[kcal/mol] |
|---------------|------------------------------------------------------|--------------------------------------------------------------------------------------|--------------------------|
| ATP1          | <chem>CN(C)c1ccc(C=CC(=O)c2cccs2)cc1</chem>          |    | -8.5                     |
| ATP2          | <chem>O=C(/C=C/C=C/c1ccccc1)c1cccc1</chem>           |   | -8.2                     |
| ATP3          | <chem>[O-][N+](=O)c1ccc(/C=C/C(=O)c2cccs2)cc1</chem> |  | -8.1                     |
| ATP4          | <chem>O=C(\C=C\c1c[nH]c2ccccc21)c1cccs1</chem>       |  | -7.5                     |
| ATP5          | <chem>O=C(\C=C\c1c2ccccc2cc2ccccc12)c1cccc1</chem>   |  | -10.0                    |

|              |                                                    |                                                                                      |      |
|--------------|----------------------------------------------------|--------------------------------------------------------------------------------------|------|
| <b>ATP6</b>  | <chem>[O-][N+](=O)c1ccccc1/C=C/C(=O)c1cccs1</chem> |    | -6.8 |
| <b>ATP7</b>  | <chem>O=C(\C=C\c1ccc(cc1)C#N)c1cccs1</chem>        |    | -7.5 |
| <b>ATP8</b>  | <chem>O=C(\C=C\c1cc(ccc1)C#N)c1cccs1</chem>        |    | -7.1 |
| <b>ATP9</b>  | <chem>O=C(\C=C\c1cccc(C)c1)c1cccs1</chem>          |   | -7.8 |
| <b>ATP10</b> | <chem>O=C(\C=C\c1cccc(CC)c1)c1cccs1</chem>         |  | -7.8 |
| <b>ATP11</b> | <chem>O=C(\C=C\c1ccccc1C#N)c1cccs1</chem>          |  | -7.5 |
| <b>ATP12</b> | <chem>O=C(\C=C\c1ccc(I)cc1)c1cccs1</chem>          |  | -6.8 |
| <b>ATP13</b> | <chem>O=C(\C=C\c1ccc(Cl)cc1Cl)c1cccs1</chem>       |  | -7.0 |

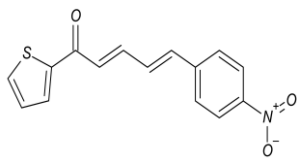
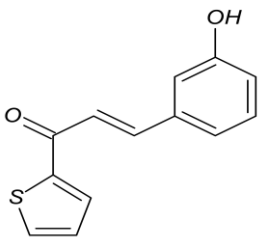
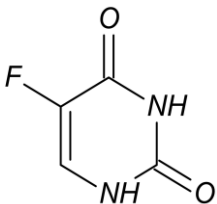
|              |                                                          |                                                                                    |      |
|--------------|----------------------------------------------------------|------------------------------------------------------------------------------------|------|
| <b>ATP14</b> | <chem>[O-][N+](=O)c1ccc(cc1)\C=C\C=C\C(=O)c1cccs1</chem> |  | -8.1 |
| <b>ATP15</b> | <chem>O=C(\C=C\c1cc(O)ccc1)c1cccs1</chem>                |  | -7.3 |
| <b>STD</b>   | <chem>O=C1NC(=O)C(F)=CN1</chem>                          |  | -4.7 |

Table 3: Lipinski's rule of five parameters of the designed compounds

| Sl.No | Compound Code | Log P | Molecular Weight | HBD | HBA | Lipinski's rule violation |
|-------|---------------|-------|------------------|-----|-----|---------------------------|
| 1     | ATP1          | 3.37  | 257.35           | 0   | 1   | 0                         |
| 2     | ATP2          | 3.92  | 240.32           | 0   | 1   | 0                         |
| 3     | ATP3          | 2.76  | 259.28           | 0   | 3   | 0                         |
| 4     | ATP4          | 3.13  | 255.33           | 1   | 1   | 0                         |
| 5     | ATP5          | 4.13  | 314.40           | 0   | 1   | 0                         |
| 6     | ATP6          | 2.83  | 259.28           | 0   | 3   | 0                         |
| 7     | ATP7          | 3.13  | 239.29           | 0   | 2   | 0                         |
| 8     | ATP8          | 3.14  | 239.29           | 0   | 2   | 0                         |
| 9     | ATP9          | 3.74  | 228.31           | 0   | 1   | 0                         |
| 10    | ATP10         | 4.04  | 242.34           | 0   | 1   | 0                         |
| 11    | ATP11         | 3.16  | 239.29           | 0   | 2   | 0                         |
| 12    | ATP12         | 4.09  | 340.18           | 0   | 1   | 0                         |
| 13    | ATP13         | 4.44  | 283.17           | 0   | 1   | 0                         |
| 14    | ATP14         | 3.30  | 285.32           | 0   | 3   | 0                         |
| 15    | ATP15         | 2.97  | 230.28           | 1   | 2   | 0                         |

|    |     |      |        |   |   |   |
|----|-----|------|--------|---|---|---|
| 16 | STD | 0.13 | 130.08 | 0 | 1 | 0 |
|----|-----|------|--------|---|---|---|

**Table 4.1: Pharmacokinetic (ADME) Properties of Selected Compounds Using pkCSM**

| Compound code | Caco-2 (log Papp) | P-gp Inhibitor | P-gp Substrate | HIA (%) | BBB (log BB) | VDss (log L/kg) | Fu    | Clearance (log ml/min/kg) |
|---------------|-------------------|----------------|----------------|---------|--------------|-----------------|-------|---------------------------|
| ATP1          | 1.192             | No             | No             | 94.783  | 0.429        | 0.373           | 0.003 | 0.128                     |
| ATP2          | 1.861             | No             | No             | 94.038  | 0.546        | 0.529           | 0     | 0.16                      |
| ATP3          | 1.36              | No             | Yes            | 92.974  | -0.256       | 0.469           | 0     | 0.051                     |
| ATP4          | 1.75              | No             | Yes            | 91.109  | 0.272        | 0.192           | 0.049 | 0.114                     |
| ATP5          | 1.67              | yes            | yes            | 97.017  | 0.753        | 0.121           | 0.176 | -0.075                    |
| ATP6          | 1.368             | No             | No             | 93.71   | -0.24        | 0.236           | 0     | 0.202                     |
| ATP7          | 1.212             | No             | No             | 94.258  | 0.086        | 0.199           | 0     | 0.12                      |
| ATP8          | 1.212             | No             | No             | 94.258  | 0.086        | 0.199           | 0     | 0.12                      |
| ATP9          | 1.684             | No             | No             | 94.916  | 0.546        | 0.527           | 0.021 | 0.098                     |
| ATP10         | 1.711             | No             | No             | 94.669  | 0.615        | 0.681           | 0     | 0.064                     |
| ATP11         | 1.265             | No             | No             | 93.95   | 0.134        | 0.297           | 0     | 0.135                     |
| ATP12         | 1.669             | No             | No             | 94.125  | 0.534        | 0.485           | 0.002 | -0.293                    |
| ATP13         | 1.543             | No             | No             | 92.528  | 0.514        | 0.519           | 0     | -0.048                    |
| ATP14         | 1.42              | No             | No             | 92.787  | -0.31        | 0.267           | 0     | 0.07                      |
| ATP15         | 1.398             | No             | No             | 92.407  | 0.094        | 0.172           | 0.12  | 0.042                     |
| STD           | 0.582             | No             | No             | 92.111  | -0.432       | -0.405          | 0.757 | 0.642                     |

**Table 4.2: Metabolism score of designed derivatives.**

| Compound Code | CYP1A2 inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 inhibitor | CYP3A4 inhibitor |
|---------------|------------------|-------------------|------------------|------------------|------------------|
| ATP1          | Yes              | Yes               | Yes              | No               | No               |
| ATP2          | Yes              | Yes               | Yes              | No               | No               |
| ATP3          | Yes              | Yes               | Yes              | No               | No               |
| ATP4          | Yes              | Yes               | Yes              | No               | No               |
| ATP5          | Yes              | Yes               | Yes              | No               | No               |
| ATP6          | Yes              | Yes               | Yes              | No               | Yes              |
| ATP7          | Yes              | Yes               | Yes              | No               | Yes              |
| ATP8          | Yes              | Yes               | Yes              | No               | Yes              |
| ATP9          | Yes              | Yes               | Yes              | No               | No               |
| ATP10         | Yes              | Yes               | Yes              | No               | Yes              |
| ATP11         | Yes              | Yes               | Yes              | No               | No               |

|              |     |     |     |    |     |
|--------------|-----|-----|-----|----|-----|
| <b>ATP12</b> | Yes | Yes | Yes | No | No  |
| <b>ATP13</b> | Yes | Yes | Yes | No | No  |
| <b>ATP14</b> | Yes | Yes | Yes | No | Yes |
| <b>ATP15</b> | Yes | Yes | No  | No | No  |
| <b>STD</b>   | No  | No  | No  | No | No  |

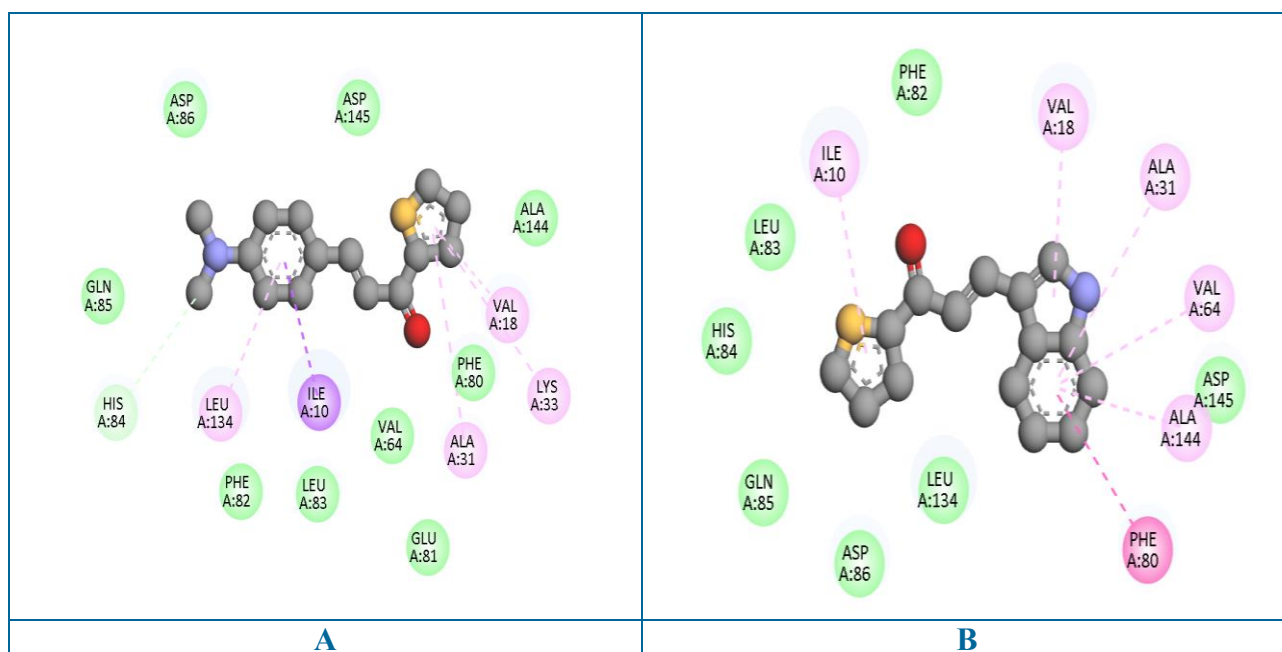
**Table 5: Physiochemical properties of the Prepared Compounds**

| <b>Compound code</b> | <b>MF</b>                                                    | <b>MR (cm<sup>3</sup>)</b> | <b>MW (g)</b> | <b>MV (cm<sup>3</sup>)</b> | <b>Density (g/cm<sup>3</sup>)</b> |
|----------------------|--------------------------------------------------------------|----------------------------|---------------|----------------------------|-----------------------------------|
| <b>ATP1</b>          | C <sub>15</sub> H <sub>15</sub> NOS                          | 79.80±0.3                  | 257.35        | 217.2±3.0                  | 1.184±0.06                        |
| <b>ATP2</b>          | C <sub>15</sub> H <sub>12</sub> OS                           | 74.81±0.3                  | 240.32        | 205.9±3.0                  | 1.166±0.06                        |
| <b>ATP3</b>          | C <sub>13</sub> H <sub>9</sub> NO <sub>3</sub> S             | 77.76±0.3                  | 259.28        | 191.1±3.0                  | 1.356±0.06                        |
| <b>ATP4</b>          | C <sub>15</sub> H <sub>11</sub> O <sub>2</sub>               | 78.31±0.3                  | 250.29        | 191.7±3.0                  | 1.321±0.06                        |
| <b>ATP5</b>          | C <sub>21</sub> H <sub>14</sub> OS                           | 101.17±0.3                 | 314.10        | 247.5±3.0                  | 1.270±0.06                        |
| <b>ATP6</b>          | C <sub>13</sub> H <sub>9</sub> NO <sub>3</sub> S             | 72.03±0.3                  | 259.27        | 191.1±3.0                  | 1.356±0.06                        |
| <b>ATP7</b>          | C <sub>14</sub> H <sub>9</sub> NOS                           | 68.08±0.4                  | 239.29        | 189±5.0                    | 1.26±0.1                          |
| <b>ATP8</b>          | C <sub>14</sub> H <sub>9</sub> NOS                           | 68.08±0.4                  | 239.29        | 189.8±5.0                  | 1.26±0.1                          |
| <b>ATP9</b>          | C <sub>14</sub> H <sub>12</sub> OS                           | 70.31±0.3                  | 228.03        | 195±3.0                    | 1.167±0.06                        |
| <b>ATP10</b>         | C <sub>15</sub> H <sub>14</sub> OS                           | 75.04±0.3                  | 242.33        | 212.1±3.0                  | 1.142±0.06                        |
| <b>ATP11</b>         | C <sub>14</sub> H <sub>9</sub> NOS                           | 68.08±0.4                  | 239.29        | 189.8±5.0                  | 1.26±0.1                          |
| <b>ATP12</b>         | C <sub>13</sub> H <sub>9</sub> IOS                           | 78.39±0.3                  | 340.17        | 201.3±3.0                  | 1.689±0.06                        |
| <b>ATP13</b>         | C <sub>13</sub> H <sub>8</sub> Cl <sub>2</sub> OS            | 75.28±0.3                  | 283.16        | 203.2±3.0                  | 1.393±0.06                        |
| <b>ATP14</b>         | C <sub>15</sub> H <sub>11</sub> NO <sub>3</sub> S            | 81.36±0.3                  | 285.31        | 217.1±3.0                  | 1.310±0.06                        |
| <b>ATP15</b>         | C <sub>13</sub> H <sub>10</sub> O <sub>2</sub> S             | 67.37±0.3                  | 230.28        | 177.7±3.0                  | 1.295±0.06                        |
| <b>STD</b>           | C <sub>4</sub> H <sub>3</sub> FN <sub>2</sub> O <sub>2</sub> | 25.85±0.4                  | 130.07        | 84.5±5.0                   | 1.53±0.1                          |

**Table 6 : Toxicological Profile of Compounds Using ProTox-3.0**

| <b>Compound code</b> | <b>LD50 (mg/kg)</b> | <b>Toxicity category</b> | <b>Hepatotoxicity</b> | <b>Carcinogenicity</b> | <b>Immunotoxicity</b> | <b>Respiratory toxicity</b> |
|----------------------|---------------------|--------------------------|-----------------------|------------------------|-----------------------|-----------------------------|
| <b>ATP1</b>          | 1800                | 4                        | -                     | -                      | -                     | +                           |
| <b>ATP2</b>          | 1800                | 4                        | -                     | +                      | -                     | -                           |
| <b>ATP3</b>          | 3000                | 5                        | +                     | +                      | -                     | -                           |

|              |      |   |   |   |   |   |
|--------------|------|---|---|---|---|---|
| <b>ATP4</b>  | 1000 | 4 | + | - | - | - |
| <b>ATP5</b>  | 1800 | 4 | - | - | - | - |
| <b>ATP6</b>  | 3000 | 5 | + | + | - | - |
| <b>ATP7</b>  | 1800 | 4 | - | - | - | - |
| <b>ATP8</b>  | 1800 | 4 | - | - | - | - |
| <b>ATP9</b>  | 1800 | 4 | - | - | - | - |
| <b>ATP10</b> | 1800 | 4 | - | + | - | - |
| <b>ATP11</b> | 1800 | 4 | - | - | - | - |
| <b>ATP12</b> | 1800 | 4 | - | - | - | - |
| <b>ATP13</b> | 1800 | 4 | - | - | - | - |
| <b>ATP14</b> | 3000 | 5 | + | + | - | - |
| <b>ATP15</b> | 1800 | 4 | + | - | - | - |
| <b>STD</b>   | 1923 | 4 | - | + | - | - |



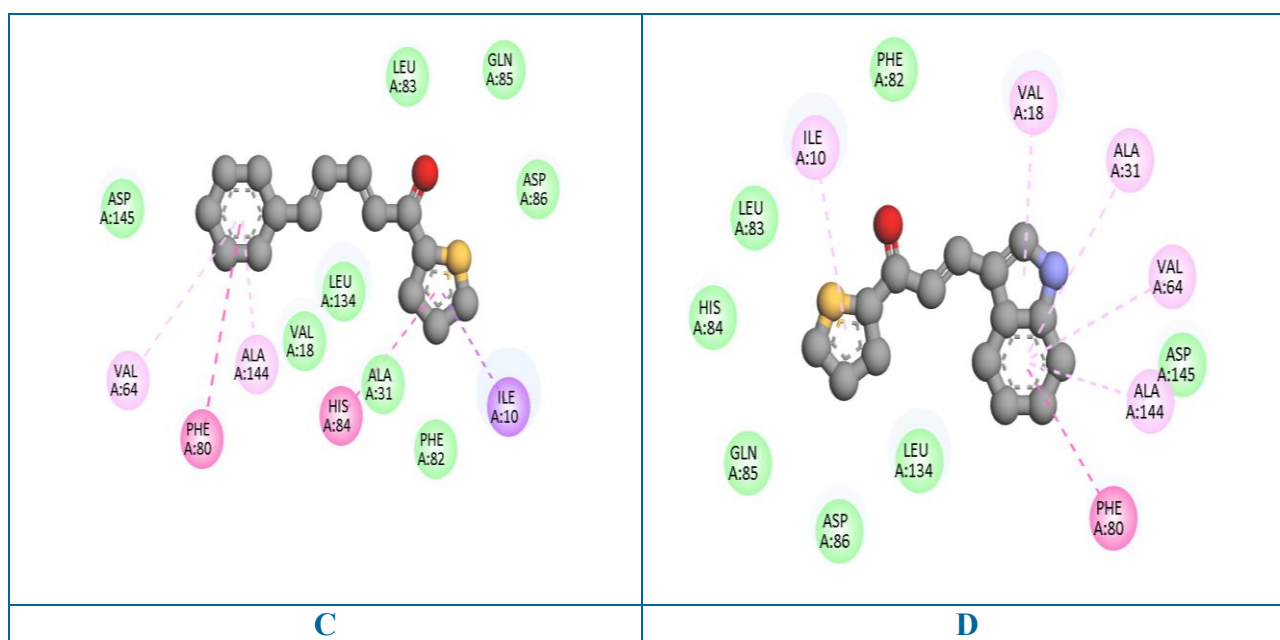


**Fig. 2: (A–D) represent the four docked compounds and their corresponding contact with the binding-site residues.**

The four docked compounds and their matching interactions with the binding-site residues are shown in (A–D). The interacting binding site residues are shown as labeled spheres, while the bioactive chemicals are represented as ball and sticks. Van der waals interactions are shown by green dashed lines; conventional hydrogen bonds are depicted by light-green dashed lines;

$\pi$ -Sigma interactions are represented by purple dashed lines;  $\pi$ -Alkyl interaction are shown by pink dashed lines;  $\pi$ -Cation interaction are represented by orange dashed lines

**Table 7: Intermolecular interactions of bioactive compounds with target protein (2FVD)**

| Compound code | Docking score | Interacting group                                             | Intermolecular interaction                                                                                              |
|---------------|---------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| <b>ATP1</b>   | -8.5          | Ile A:10<br>Val A:18<br>Ala A:31<br>His A:84                  | $\pi$ - sigma<br>$\pi$ - Alkyl<br>$\pi$ - Alkyl<br>Carbon-Hydrogen bond                                                 |
| <b>ATP2</b>   | -8.2          | Tyr A:269<br>His A:268<br>Trp A:243<br>Arg A:245<br>Val A:226 | Conventional Hydrogen Bond<br>Conventional Hydrogen Bond<br>Conventional Hydrogen Bond<br>$\pi$ -Cation<br>$\pi$ -Sigma |
| <b>ATP3</b>   | -7.2          | Phe A:80<br>Ile A:10<br>Val A:18<br>Ala A:31                  | $\pi$ - $\pi$ Stacked<br>$\pi$ -Alkyl<br>$\pi$ -Alkyl<br>$\pi$ -Alkyl                                                   |

|      |      |                                                           |                                                                                               |
|------|------|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------|
|      |      | Val A:64                                                  | $\pi$ -Alkyl                                                                                  |
| ATP4 | -7.4 | Phe A:80<br>His A:84<br>Ile A:10<br>Val A:64<br>Ala A:144 | $\pi$ - $\pi$ Stacked<br>Amide- $\pi$ Stacked<br>$\pi$ -Sigma<br>$\pi$ -Alkyl<br>$\pi$ -Alkyl |

#### 4. DISCUSSION

The current investigation showed that the thiophene-based chalcone derivatives had intriguing pharmacological and drug-like properties. With appropriate molecular weights, hydrogen-bonding characteristics, and moderate lipophilicity, every molecule exhibited zero breaches of Lipinski's Rule of Five. For the majority of derivatives, in silico ADME analysis demonstrated good intestinal absorption and permeability; nevertheless, certain compounds displayed possible P-glycoprotein and CYP450 interactions that need more research. The necessity for experimental safety study was highlighted by toxicity prediction, which showed moderate acute toxicity and certain chemicals with anticipated hepatotoxicity or carcinogenicity. The designed compounds showed excellent interactions with the binding-site residues in molecular docking tests against the target protein 2FVD. ATP1 has the greatest docking score (-8.5 kcal/mol) among all the compounds that were tested, followed by ATP2 (-8.2 kcal/mol). With important amino acid

residues, the docked molecules generated a variety of stabilizing contacts, including as hydrogen bonding,  $\pi$ - $\pi$ ,  $\pi$ -alkyl,  $\pi$ -sigma and van der Waals interactions. Thiophene-based chalcone derivatives, especially ATP1, may be interesting lead compounds for additional research as possible CDK inhibitors, according to the combined physicochemical, ADME, toxicity, and molecular docking studies. To validate these computational results, however, experimental biological and toxicological investigations are needed.

#### 5. CONCLUSION

Through physicochemical studies, in silico ADME and toxicity prediction, and molecular docking studies, the current study effectively investigated a number of thiophene-based

chalcone derivatives as possible CDK inhibitors. With no breaches of Lipinski's Rule of Five and usually good projected intestinal absorption, the designed compounds demonstrated acceptable drug-like characteristics. Positive ligand-protein interactions were shown by molecular docking against the target protein 2FVD, with ATP1 exhibiting the highest binding affinity with a docking score of -8.5 kcal/mol. The overall results point to thiophene-based chalcone derivatives, especially ATP1, as interesting lead molecules for additional research, even if some compounds displayed anticipated metabolic and toxicity issues. To confirm their safety profile and CDK inhibitory capabilities, more experimental biology, pharmacokinetic, and toxicological research is needed.

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