Original Article

Thiophenebearing pyrimidine derivatives synthesis from chalcones: In silico ADME/T studies and molecular docking studies

K. Neelaveni*1, Y. Rajendra Prasad2 and K. Krishna3

1*Research Scholar, AacharyaNagarjuna University, Guntur, Andhra Pradesh, India.
Assistant Professor, CMR College of Pharmacy, Hyderabad, Telangana, India.
2Professor, AU College of Pharmaceutical Sciences, Visakahapatnam, Andhra Pradesh, India.
3Associate Professor, DCRM College of Pharmacy, Inkollu, Andhra Pradesh, India.
Email: 1neelaveni210@gmail.com
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Abstract

Thiophene bearing pyrimidines were synthesized from chalcones using designed synthesis procedure. Reaction of substituted acetophenones and thiophene-2-carbaldehyde gives chalcones. Further chalcones upon reaction with urea gives thiophene bearing pyrimidine derivatives. The developed thiophene bearing pyrimidine derivatives were characterized by physical and spectral analysis. Using the SwissADME web tool, the in silico ADME/Toxicity properties of the novel compounds were calculated, and the results showed sufficient values of absorption, distribution, and excretion, parameters relevant to bioavailability. Low estimates of toxicity were also suggested for these substances. In order to forecast anti-inflammatory effects, molecular docking experiments were conducted at the protein targets for cyclooxygenases (PDB IDs 3KK6 and 5IKR). Overall yields of the compounds were good, and molecular docking suggested that they would bind to 3KK6 and 5IKR favourably.

Keywords: substituted acetophenones, thiophene-2-carbaldehyde, chalcones, thiophene bearing pyrimidines, ADME/Toxicity properties, docking studies.

INTRODUCTION

A number of significant biological molecules, commonly referred to as chalcones or chalconoids, have chalcone as its major component. Chalcone is an aromatic ketone and an enone. Because the chromophore -CO-CH=CH- is present, these compounds have colour. Chalcones possess an excellent synthon, allowing for the design of a wide range of new heterocycles with favourable medicinal properties. An aromatic aldehyde and an aromatic ketone can be combined in a Claisen-Schmidt reaction with sodium hydroxide acting as a catalyst to produce chalcones. Chalcones are widely used as intermediates in the synthesis of several heterocyclic compounds. Chalcone is cyclized to produce heterocyclic compounds with nitrogen-containing rings, such as pyrazolines and pyrimidines, which have gained popularity due to their potential as pharmaceuticals [**1-3**].

Pyrimidines hold a unique place due to their predominate usage within the diverse spectrum of biological applications for heterocyclic compounds. Pyrimidines are well-known and significant six-membered heterocyclic compounds that contain nitrogen. The discovery that certain pyrimidine derivatives have strong biological activities has sparked interest in this area of study. Due to their intriguing biological actions, pyrimidines and substituted pyrimidines have received a lot of research [**4-6**]. Pyrimidine derivatives have been fundamental to the development of heterocyclic Pyrimidines exhibit a wide range of potential pharmacological activities and are found in many pharmacologically active molecules, including pyrimethamine, trimethoprim, zidovudine, zalcitabine, pyrantel, buspirone, uracil, cytosine, cytidine, uridine, barbiturates, 5-fluorouracil, cytarabine, tegafur, imatinib etc. The anticancer, antidepressant, antibacterial, antihelmintic, anticonvulsant, antitumor, antifungal, anti-tubercular, anti-inflammatory, analgesic, antiamoebic, antimycobacterial, herbicidal, anti-malarial, and antihistamic properties of pyrimidine derivatives have been well established with pyrimidine derivatives [**7, 8**].

In this study, substituted acetophenones and thiophene-2-carbaldehyde were combined in the Claisen-Schmidt condensation to create chalcone scaffolds containing thiophene. The created chalcones were also utilised as the main starting material for the cyclization of urea to produce thiophene containing pyrimidine derivatives. Novel thiophene containing pyrimidine derivatives that were designed and produced were examined for their spectroscopic and physical characteristics. *In silico* ADME/Toxicity characteristics and molecular docking investigations at cyclooxygenase protein targets were performed to predict their anti-inflammatory action.

MATERIALS AND METHODS

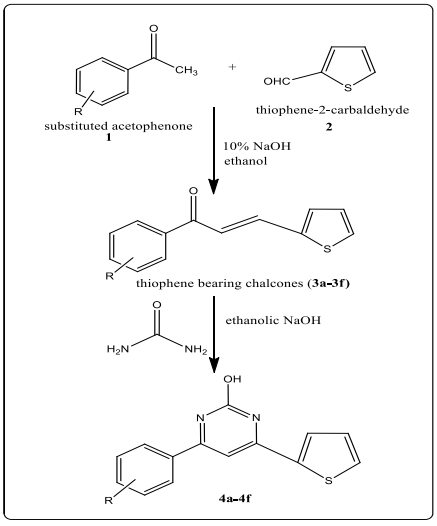
Chemicals and reagents were procured from commercial vendors Merck and AVRA, which were employed for the synthesis of novel pyrimidine derivatives; these materials were not purified before use. With the use of E.Merck grade silica gel 60GF-254 pre-coated plates, thin layer chromatography was used to monitor both the reaction's progress and completion. Electrical melting point apparatus was used to determine melting points, which were then left uncorrected. IR spectra [KBr in cm^{-1}] of the substances were captured using the KBr pellet technique in a Bruker FT-IR spectrophotometer. On a Bruker-AMX spectrophotometer operating at 400MHz, chemical shifts in ppm of 1H-NMR spectra were noted in relation to tetramethylsilane (TMS) as the internal standard. The Agilent-LC-MSD-1200 mass spectrometer used to record mass spectra. Reagents and chemicals utilized for the synthesis of novel pyrimidine derivatives were obtained from commercial suppliers Merck, AVRA and those were used without purification. Progress of the reaction as well as completion of the reaction was monitored by thin layer chromatography with the help of E.Merck grade silica gel 60GF-254 pre-coated plates. Melting points were determined by using electrical melting point apparatus and were uncorrected. IR spectra [KBr ν in cm^{-1}] of the compounds were recorded in Bruker FT-IR spectrophotometer using KBr pellet technique. Chemical shifts in ppm of ^{1}H-NMR spectra were recorded on Bruker-AMX spectrophotometer at 400MHz in relation to tetramethylsilane (TMS) as internal standard. The mass spectra recorded on Agilent-LC-MSD-1200 mass spectrometer. The SwissADME online programme was used to conduct in silico ADME/Toxicity investigations. Using the software programmes AutoDockVina, ChemDraw, and BIOVIA discovery studio, molecular docking investigations were performed at several target protein active sites.

Synthesis of thiophene bearing chalcone derivatives 3a-3f [9, 10]

Substituted acetophenones**1** (0.01mol) and thiophene-3-carbaldehyde **2** (0.01mol) were combined via Claisen-Schmidt condensation in 20 ml of ethanol with 20% NaOH acting as a catalyst. At room temperature, the reaction mixture was stirred. After the reaction is finished, the mixture is poured onto crushed ice along with a little amount of diluted HCl to neutralise the sodium hydroxide. The solid is then dried and recrystallized from ethanol after being filtered and rinsed with cold water.

Synthesis of thiophene bearing pyrimidine derivatives from chalcones 4a-4f [11, 12]

The preparation of thiopheene baring pyrimidine derivatives involves the reaction of prepared chalcones**3a-3f** (0.01 mol) with urea (0.01 mol). A mixture of chalcone (0.01 mol), urea (0.01 mol), ethanolicNaOH (5 g of NaOH in 25 ml ethanol) was refluxed for 15-18 hrs. The reaction progress was monitored by TLC. Filtered, ice-cold water was used to wash the precipitate, and it was then dried. The solid substance was purified by recrystallization from ethanol.



R = **4a:** 4-OH **4d:** 4-Cl

4b: 4-OCH_3 **4e:** 4-Br

4c: 4-NH_2 **4f:** 3-NO_2

Scheme: Thiophene bearing pyrimidine derivatives synthesis from Chalcones

4a: 4-(4-hydroxyphenyl)-6-(thiophen-2-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3558 (phenolic-OH str.), 3697 (pyrimidine-OH str.), 3012 (aromatic =C-H str.), 1525 (aromatic C=C str.), 1618 (C=N str.), 622 (C-S str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 5.38 (1H, s, phenolic-O<u>H</u>), 7.78 (1H, s, pyrimidine-O<u>H</u>), 6.82-6.95 (2H, d, phenyl-C_2-H & C_6-H), 7.54-7.68 (2H, d, phenyl-C_3-H & C_5-H), 7.51 (1H, s, pyrimidine-C_5-H), 8.30-8.45 (1H, d, thiophene- C_3-H), 7.18-7.41 (1H, t, thiophene-C_4-H), 7.92-8.18 (1H, d, thiophene- C_5-H). ESI-MS: m/z (M^+) 270.12

4b: 4-(4-methoxyphenyl)-6-(thiophen-2-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3725 (pyrimidine-OH str.), 3029 (aromatic =C-H str.), 2916 (-CH- str.), 1521 (aromatic C=C str.), 1635 (C=N str.), 617 (C-S str.), 1236 (ether C-O str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 3.45 (3H, s, -OC<u>H</u>$_3$), 7.85 (1H, s, pyrimidine-O<u>H</u>), 7.05-7.18 (2H, d, phenyl-C_2-H & C_6-H), 7.58-7.71 (2H, d, phenyl-C_3-H & C_5-H), 7.99 (1H, s, pyrimidine-C_5-H), 8.40-8.55 (1H, d, thiophene- C_3-H), 7.21-7.49 (1H, t, thiophene- C_4-H), 8.11-8.25 (1H, d, thiophene- C_5-H). ESI-MS: m/z (M^+) 284.11

4c: 4-(4-aminophenyl)-6-(thiophen-2-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3652 (pyrimidine-OH str.), 3541, 3523.38 (primary amine -NH- str.), 3059 (aromatic =C-H str.), 1518 (aromatic C=C str.), 1613 (C=N str.), 628 (C-S str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 6.27 (2H, s, -N<u>H</u>$_2$), 7.81 (1H, s, pyrimidine-O<u>H</u>), 6.91-7.12 (2H, d, phenyl-C_2-H & C_6-H), 7.41-7.53 (2H, d, phenyl-C_3-H & C_5-H), 7.73 (1H, s, pyrimidine-C_5-H), 8.18-8.30 (1H, d, thiophene- C_3-H), 7.13-7.39 (1H, t, thiophene-C_4-H), 8.41-8.57 (1H, d, thiophene- C_5-H). ESI-MS: m/z (M^+) 269.08

4d: 4-(4-chlorophenyl)-6-(thiophen-2-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3635 (pyrimidine-OH str.), 3081 (aromatic =C-H str.), 1526 (aromatic C=C str.), 1632 (C=N str.), 620 (C-S str.), 709 (C-Cl str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 7.83 (1H, s, pyrimidine-O<u>H</u>), 7.33-7.47 (2H, d, phenyl-C_2-H & C_6-H), 7.98-8.15 (2H, d, phenyl-C_3-H & C_5-H), 7.70 (1H, s, pyrimidine-C_5-H), 8.20-8.31 (1H, d, thiophene- C_3-H), 7.56-7.75 (1H, t, thiophene- C_4-H), 8.41-8.56 (1H, d, thiophene- C_5-H). ESI-MS: m/z (M^+) 288.04

4e: 4-(4-bromophenyl)-6-(thiophen-2-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3622 (pyrimidine-OH str.), 3074 (aromatic =C-H str.), 1518 (aromatic C=C str.), 1614 (C=N str.), 620 (C-S str.), 564 (C-Br str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 7.91 (1H, s, pyrimidine-O<u>H</u>), 7.37-7.49 (2H, d, phenyl-C_2-H & C_6-H), 8.11-8.26 (2H, d, phenyl-C_3-H & C_5-H), 7.80 (1H, s, pyrimidine-C_5-H), 8.31-8.43 (1H, d, thiophene- C_3-H), 7.62-7.84 (1H, t, thiophene- C_4-H), 8.47-8.59 (1H, d, thiophene- C_5-H). ESI-MS: m/z (M^+) 333.96

4f: 4-(4-nitrophenyl)-6-(thiophen-2-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3605 (pyrimidine-OH str.), 1541 & 1378 (nitro N-O str.), 3092 (aromatic =C-H str.), 1541 (aromatic C=C str.), 1643 (C=N str.), 628 (C-S str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 7.88 (1H, s, pyrimidine-O<u>H</u>), 8.05-8.17 (2H, d, phenyl-C_2-H & C_6-H), 8.46-8.58 (2H, d, phenyl-C_3-H & C_5-H), 7.95 (1H, s, pyrimidine-C_5-H), 7.51-7.64 (1H, d, thiophene- C_3-H), 7.32-7.56 (1H, t, thiophene- C_4-H), 7.73.-7.85 (1H, d, thiophene- C_5-H). ESI-MS: m/z (M^+) 299.06

ADME/Toxicity Studies [13-15]

A computer tool called ADMET Predictor was created for calculating the pharmacokinetic parameters and characteristics of drug-like compounds based on their molecular structures. ADMET stands for Absorption, Distribution, Metabolism, Excretion/Elimination, and Toxicity. A molecule does not automatically qualify as a promising candidate just because it is highly bioactive and has a low hazardous profile. In the process of discovering new drugs and drugs like compounds, a novel chemical should only be explored if it has a better pharmacokinetic profile. To prevent wasting time or resources, it is crucial to assess the ADMET profile of novel compounds as soon as possible. As a result, we used the online swissADME software to predict the ADMET properties of our developed molecules (**4a**–**4f**). The Lipinski "Rule of Five" was the "most widely utilised rule-based filter" of drug-likeness and was used to determine whether a molecule is well absorbed orally. Molecular weight (MW) ≤ 500, Octanol/water partition coefficient (iLOGP) ≤ 5, Number of hydrogen bond donors (HBDs) ≤ 5, and Number of hydrogen bond acceptors (HBAs) ≤ 10.6 are the components of the rule of five.

The four rules of five (MW, iLOGP, HBAs, and HBDs) and four additional parameters, including molecular topological polar surface area (TPSA), number of rotatable bonds (RB), number of aromatic heavy atoms

(nAH), and number of alerts for undesirable substructures, were generated by the quantitative estimate of drug-likeness (QED) concept (ALERTs). Comparing the concept of QED to standard drug-likeness principles, the latter is the more adaptable and widely used. The following list includes certain ADMET features and parameters along with their permitted limits.

Table-1: *Permitted limits of ADMET parameters*

ADMET Parameter	**Permitted limit**
Molecular weight (MW)	50 to100
octanol/water partition coefficient (iLOGP)	-2 to 10
Topological Polar Surface Area (TPSA)	20 to 130
Number of H-Bond acceptors (HBA)	0 to 10
Number of H-bond Donors (HBD)	0 to 5
Rotatable bonds (RB)	0 to 5
Number of aromatic heavy atoms (nAH)	15 to 50
Lipophilicity of the compound (LogP)	-0.7 to 5.0
Molar refractivity (MR)	40 to 130

Chemdraw Ultra 12.0 was used to draw the 2D structures of the compounds in order to assess the pharmacokinetic characteristics of the developed compounds. Each structure was imported, and the interface of the website (http://swissadme.ch/) required the entry of the structure smiley. The ADMET properties/parameters were obtained by the SwissADME drug design project.

Molecular Docking Studies

In order to identify possible anti-inflammatory drugs, molecular docking experiments were carried out on the cyclooxygenase-1 (COX-1), and cyclooxygenase-2 (COX-2) target proteins. Download the PDB files for the 3D crystal structures of cyclooxegenase-1 PDB ID: 3KK6 [**16-18**] and cyclooxegenase-2 PDB ID: 5IKR [**19-21**] from the RCBS Protein Data Bank (https://www.rcsb.org/). Using BIOVIA Discovery studio visualizer 2021, the obtained proteins were made ready for docking by having water molecules and heteroatoms removed. By adding Kollman charges, Gasteiger charges, and polar hydrogens, the protein structures were reduced to the lowest energy state for further investigation. ChemDraw Ultra 12.0 was used to create the intended and produced ligand structures, and Chem 3D-Pro 12.0 was used to reduce and store the structures in SDF file format. From the PubChem database, the Diclofenac standard ligand structure SDF file format (Pubchem Id: 3033) was downloaded. Additionally, using the Open Babel software, all SDF format files are translated to PDB format. Protein transformations from PDB to PDBQT file format, grid-based docking studies using default parameters, and docking by connecting the protein-ligand using MGL AutodockVina were all completed. Using command prompt, it was possible to see the docking positions of ligands that best linked to the active site areas of the proteins. The bindings of the ligands to the target proteins in two dimensional and three dimensional were viewed using BIOVIA Discovery Studio 2021.

RESULTS AND DISCUSSION

According to the methods described in the literature, the Claisen-Schmidt reaction between substituted acetophenones and thiophene-2-carbaldehyde was initially used to create chalcones (**3a-3f**). Chalcones that have been treated with urea are subjected to cyclization to produce derivatives of pyrimidine bearing thiophene (**4a-4f**). Process of the synthesis of chalcones and thiophene containing pyrimidine derivatives wasdepicted in Scheme. **Table-2** displayed the physical characterisation data.

Table-2: *Physical characterization data of thiophene bearing pyrimidine derivatives* ***4a-4f***

Compd.	**R**	**m.p. (ºC)**	**Molecular formula**	**mol.wt.**	**% yield**	**reaction time**	**R_f value**
4a	4-hydroxy	178-180	$C_{14}H_{10}N_2O_2S$	270.31	79.54	16.5 hrs	0.61
4b	4-methoxy	166-168	$C_{15}H_{12}N_2O_2S$	284.33	70.46	17 hrs	0.59
4c	4-amino	170-172	$C_{14}H_{11}N_3OS$	269.32	81.22	15.5 hrs	0.53
4d	4-chloro	162-164	$C_{14}H_9N_2OSCl$	288.75	69.57	17.5 hrs	0.56
4e	4-bromo	154-156	$C_{14}H_9N_2OSBr$	333.20	74.28	16 hrs	0.60
4f	4-nitro	174-176	$C_{14}H_9N_3O_3S$	299.30	78.63	16.5 hrs	0.52

Results of ADMET

The results of the ADMET revealed the physicochemical properties of the designed compounds, including molecular weight (MW), number of rotatable bonds (RB), number of hydrogen donors (HBD), number of hydrogen acceptors (HBA), topological polar surface area (TPSA), octanol/water partition coefficient (iLOGP), number of aromatic heavy atoms (nAH), molar refractivity (MR), lipophilicity (LogP) and the number of alerts for undesirable substructures/ (PAINS and Brenk) were mentioned in **Table-3**. All of the created compounds agreed the rules by causing no more than one violation. All of the MW, RB, HBD, HBA, TPSA, iLOGP, nAH, and MR, in other words, are within the allowable bounds. Additionally, there is just 1 Brenk for compounds **4c**

and **4f** and no warning for PAINS, indicating the compounds high specificity. Thus, it is now possible to state that developed molecules have a favourable pharmacokinetic profile.

Table-3: *Predicted ADME parameters of thiophene bearing pyrimidines 4a-4f*

Comp.	MW	iLOGP	HBD	HBA	TPSA	RB	nAH	MR	LogP	PAINS	Brenk
4a	270.31	2.22	2	4	94.48	2	17	74.30	2.69	0	0
4b	284.33	2.75	1	4	83.48	3	17	79.30	3.08	0	0
4c	269.32	2.11	2	3	100.27	2	17	77.21	2.54	0	1
4d	288.75	2.88	1	3	74.25	2	17	77.81	3.66	0	0
4e	333.20	2.98	1	3	74.25	2	17	80.50	3.74	0	0
4f	299.30	1.73	1	5	120.07	3	17	81.63	2.24	0	1

Molecular docking results

Anti-inflammatory activities have been predicted computationally by performing molecular docking studies.

Docking at PDB structure of cyclooxegenase-1 (PDB ID: 3KK6)

In comparison to the standard ligand Diclofenac, designed ligands were evaluated at the cyclooxegenase-1 (3KK6) active site domain. **Table-4**, **Figure-1,** and **Figure-2** display the screening outcomes for the cyclooxegenase-1 protein 3KK6 using both the proposed ligands and the reference ligand Diclofenac. The conventional ligand Diclofenac was shown to have a lower docking energy −4.11 kcal/mol at the active site region than the specified ligand **4d** docking energy −4.93 kcal/mol, which suggests that significant more likely ligand at the cyclooxegenase-1 target protein.

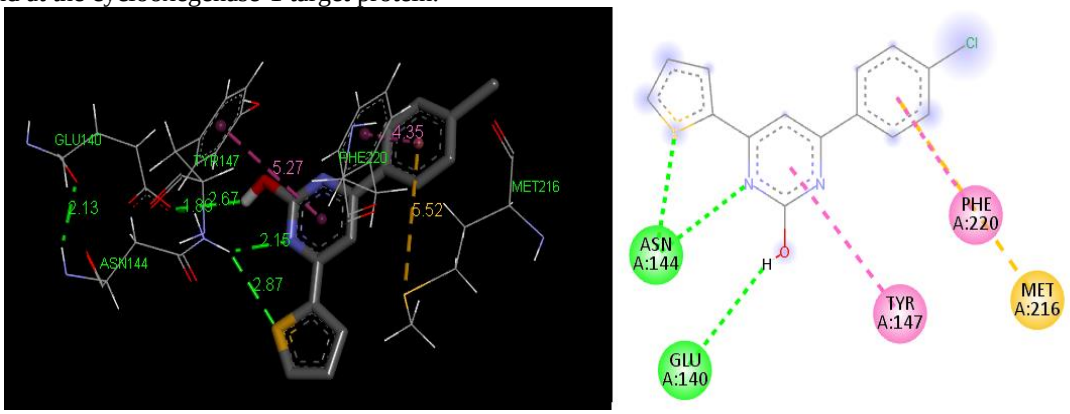


Figure-1: *3D & 2D binding mode of designed ligand compounds* ***4d*** *atactive site region of cyclooxegenase-1 protein PDB ID- 3KK6*

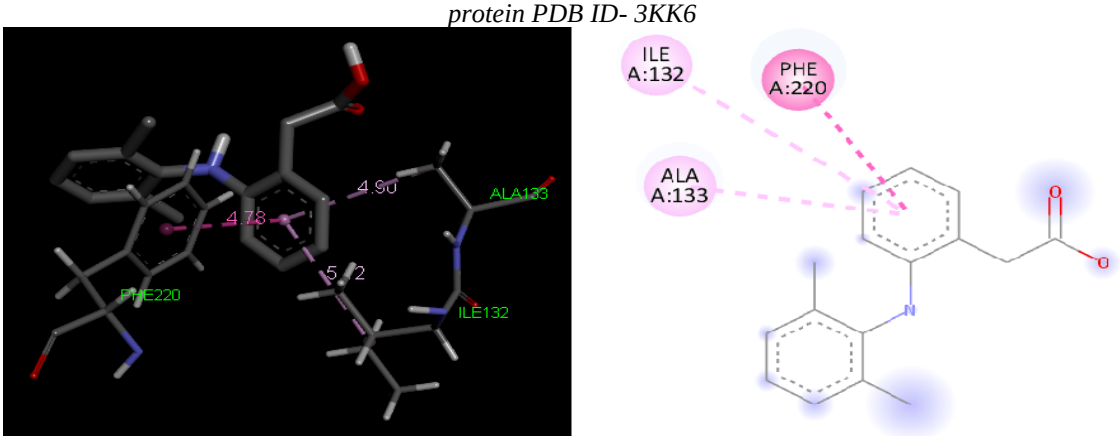


Figure-2: *3D & 2D binding mode of standard ligand Diclofenac at active site region of cyclooxegenase-1 protein PDB ID- 3KK6*

Table-4: *Binding energy & amino acid residues interacted with COX-1 protein target PDB ID – 3KK6.*

Compound	Binding energy (kcal/mol)	Interacted amino acid residues
Diclofenac	-4.11	Phe220, Ala133, Ile132
4a	-3.98	Tyr228, Leu198, Cys285, Gly215, Met156
4b	-3.87	Arg192, Val156, Ser200, Gln210
4c	-3.59	Cys185, His170, Phe220, Ala148
4d	-4.93	Glu140, Asn144, Tyr147, Met216, Phe220

4e	-4.22	Arg195, Ile210, Leu215, Ser147
4f	-4.07	Gly244, Ile190, Arg247, Leu184

Docking at PDB structure of cyclooxegenase-2 (PDB ID: 5IKR)

In comparison to the standard ligand Diclofenac, designed ligands were evaluated at the cyclooxegenase-2 (5IKR) active site domain. **Table-5, Figure-3,** and **Figure-4** display the screening outcomes for the cyclooxegenase-1 protein 3KK6 using both the proposed ligands and the reference ligand Diclofenac. The conventional ligand Diclofenac was shown to have a lower docking energy −4.31 kcal/mol at the active site region than the specified ligand **4d** docking energy −5.12 kcal/mol, which suggests that significant more likely ligand at the cyclooxegenase-2 target protein.

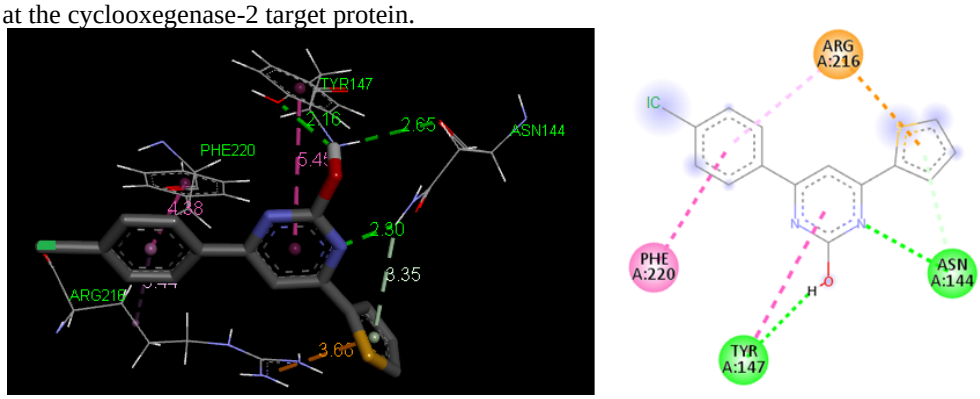


Figure-3: *3D & 2D binding mode of designed ligand compounds* ***4d*** *atactive site region of cyclooxegenase-2 proteinPDB ID- 5IKR*

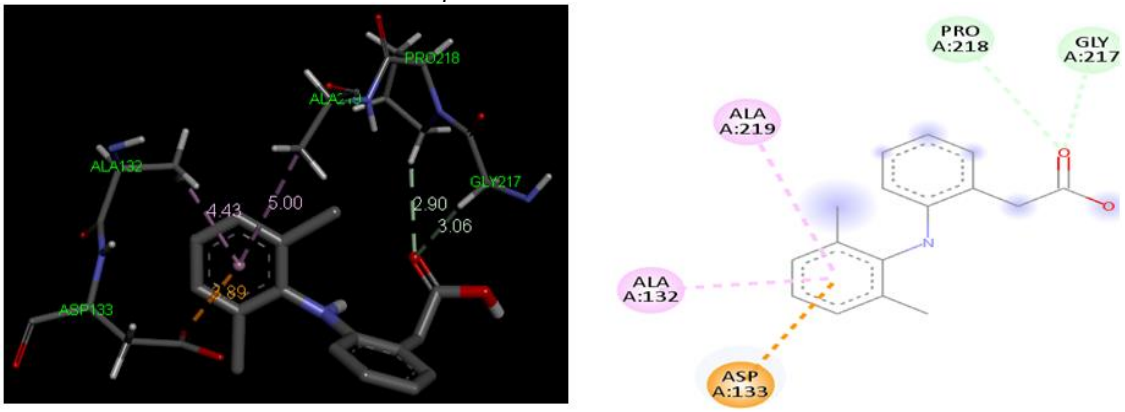


Figure-4: *3D & 2D binding mode of standard ligand Diclofenac at active site region of cyclooxegenase-2 proteinPDB ID- 5IKR*

Table-5: *Binding energy & amino acid residues interacted with COX-2 protein target PDB ID – 5IKR.*

Compound	**Binding energy (kcal/mol)**	**Interacted amino acid residues**
Diclofenac	-4.31	Gly217, Ala132, Pro218, Ala219, Asp133
4a	-3.57	Met147, Gln210, Lys190, Thr225
4b	-3.81	Ile164, His225, Tyr188, Val210
4c	-3.66	Cys214, Glu321, Met180, His145
4d	-5.12	Phe220, Asn144, Tyr147, Arg216
4e	-4.28	Val210, Arg197, Leu242, Tyr257, Ser312
4f	-4.15	Leu224, His212, Val155, Ser224, Phe196

CONCLUSION

The investigation involved the design and synthesis of a number of new pyrimidine derivatives **4a–4f** having thiophene moiety. The chemicals were physically and spectrally characterised. The proposed compounds also had a decent pharmacokinetics profile, according to an ADME/T investigation. Additionally, all the compounds were subjected to a molecular docking analysis to provide insight into structure-based design. The majority of the compound ligands had good inhibitory action against the target COX-1 and COX-2 proteins, according to the docking scores, while compound **4d** had the highest binding affinity, making it a superior lead chemical for creating potent and secure anti-inflammatory drugs.

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CONFLICT OF INTEREST
The authors declare that they do not have any conflict of interest related to the matter or content discussed in this original research article.

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