Indole moiety bearing Pyrimidines: Synthesis, Characterization and their *insilico* molecular docking studies

K. Neelaveni*[,1], Y. Rajendra Prasad[2] and K. Krishna[3]

*Research Scholar, Aacharya Nagarjuna University, Guntur, Andhra Pradesh, India.

[1]Assistant Professor, CMR College of Pharmacy, Hyderabad-501401, Telangana, India.

[2]Professor, AU College of Pharmaceutical Sciences, Visakahapatnam-530003, Andhra Pradesh, India.

3 Associate Professor, DCRM College of Pharmacy, Inkollu-523167, Andhra Pradesh, India.

* **Corresponding author Email**: neelaveni210@gmail.com

ABSTRACT

A novel indole moiety bearing pyrimidines were synthesized from chalcones using designed synthesis procedure, reaction of substituted acetophenones and indole-3-aldehyde. Further synthesized chalcones upon reaction with urea gives novel pyrimidine derivatives bearing indole moiety. The developed indole bearing pyrimidine derivatives were characterized by physical and spectral analysis. Molecular docking studies were carried out at various targets using AutoDock Vina software and revealed that some pyrimidine derivatives exhibit significant binding interaction with the active site regions of cyclooxegenase-1 (PDB ID: 3KK6), cyclooxegenase-2 (PDB ID: 5IKR) in comparison to standard ligands.

Keywords: *acetophenones, indole-3-aldehyde, chalcones, pyrimidines, docking*

INTRODUCTION

Heterocyclic compounds particularly five or six membered ring compounds have occupied the first place among various classes of organic compounds for their diverse biological activities. Pyrimidine and their derivatives have been found to possess a broad spectrum of biological activities such as antimicrobial, anti-inflammatory, analgesic, antiviral, and anticancer activities.[1] Chalcone compounds are known intermediates to prepare various heterocyclic compounds. The backbone of chalcones with the compounds has been reported to possess various biological activities such as immunomodulatory, anti-inflammatory, inhibition of aldose reductase activities, and inhibition of leukotriene B4. Pyrimidines are one of the heterocyclic compounds containing of six-membered unsaturated ring structures composed of two nitrogen atoms at position 1 and 3. Pyrimidines have been subjected to a large number of different modifications to obtain derivatives having different biological properties.[2-4] Chalcone is a simple structure that has been widely used as an effective template in drug discovery. Chalcone scaffold is a well-known precursor for the synthesis of various heterocyclic compounds. Cyclization of chalcone leads to heterocyclic compounds bearing nitrogen-containing rings such as pyrazolines and pyrimidines have gained prominence because of their potential pharmaceutical values.[5-7]

In this research work, indole bearing chalcone scaffolds were prepared by the Claisen-Schmidt condensation of substituted acetophenones and indole-3-aldehyde. Further the developed chalcones were used as key starting material for obtaining novel pyrimidine derivatives by the cyclization with urea. Designed novel pyrimidine derivatives were characterized for their physical and spectroscopic properties. Further mmolecular docking studies were carried out at the active site regions of cyclooxegenase-1 (PDB ID: 3KK6), cyclooxegenase-2 (PDB ID: 5IKR) in comparison to standard ligands.

MATERIALS AND METHODS

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 400 MHz in relation to tetramethylsilane (TMS) as internal standard. The mass spectra recorded on Agilent-LC-MSD-1200 mass spectrometer. Molecular docking studies were carried out at various target protein active sites using AutoDock Vina, ChemDraw, BIOVIA discovery studio softwares to observe binding interactions in comparison with standard ligand.

Synthesis of indole bearing chalcone derivatives [8, 9]

Claisen-Schmidt condensation (**Scheme-1**) of substituted acetophenone **1** (0.01mol) with indole-3-aldehyde **2** (0.01 mol) in 20 ml of ethanol in the presence of 20% NaOH as a catalyst. The reaction mixture was stirred at room temperature for 6–18 hrs. Progress of the reaction was monitored by TLC. The precipitate formed was filtered, washed with cold water,

and dried to give a yellow solid. The solid product was recrystallized from methanol gives yellow powder.

Synthesis of indole bearing pyrimidine derivatives from chalcones [10-13]

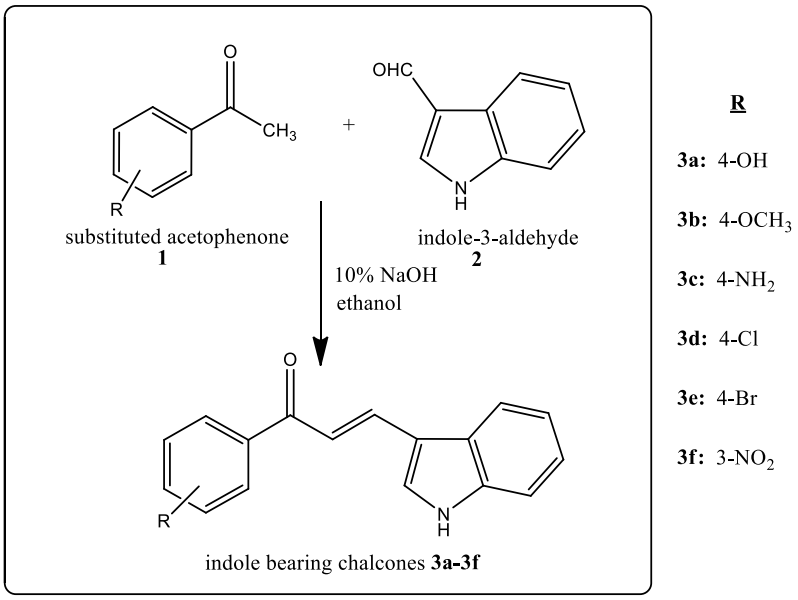
The preparation of pyrimidine derivatives involves the reaction of chalcone **3a-3f** (0.01 mol) with urea (0.01 mol) separately (**Scheme-2**). A mixture of chalcone (0.01 mol), urea/thiourea (0.01 mol), ethanolic NaOH (5 g of NaOH in 25 ml ethanol) was refluxed for 15-20 hrs. The reaction progress was monitored by TLC. The precipitate formed was filtered, washed with ice cold water, and dried. The solid product was recrystallized from ethanol.

4a: 4-(4-hydroxyphenyl)-6-(1*H*-indol-3-yl)-pyrimidin-2-ol

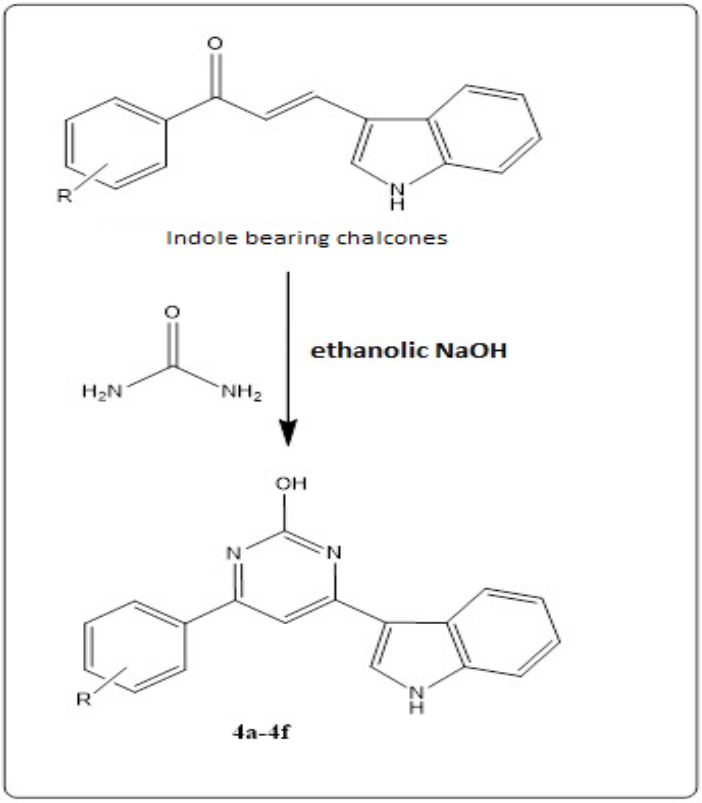
IR [KBr ν cm^{-1}]: 3616.76 (phenolic-OH str.), 3742.96 (pyrimidine-OH str.), 3395.32 (indole-NH- str.), 3014.57 (aromatic =C-H str.), 1513.92 (aromatic C=C str.), 1603.66 (C=N str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 5.35 (1H, s, phenolic-OH), 7.56 (1H, s, pyrimidine-OH), 11.46 (1H, s, indole-NH-), 6.86-6.98 (2H, d, phenyl-C_2-H & C_6-H), 7.49-7.55 (2H, d, phenyl-C_3-H & C_5-H), 7.69 (1H, s, pyrimidine-C_5-H), 7.01-8.61 (5H, m, indole-Ar-H). ESI-MS: m/z (M^+) 303.10

4b: 4-(4-methoxyphenyl)-6-(1*H*-indol-3-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3738.85 (pyrimidine-OH str.), 3396.13 (indole-NH- str.), 3070.86 (aromatic =C-H str.), 2890.33 (-CH- str.), 1514.77 (aromatic C=C str.), 1604.22 (C=N str.), 1289.02 (ether C-O str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 3.83 (3H, s, -OCH_3), 7.82 (1H, s, pyrimidine-OH), 11.58 (1H, s, indole-NH-), 7.05-7.16 (2H, d, phenyl-C_2-H & C_6-H), 7.54-7.64 (2H, d, phenyl-C_3-H & C_5-H), 7.70 (1H, s, pyrimidine-C_5-H), 7.23-8.64 (5H, m, indole-Ar-H). ESI-MS: m/z (M^+) 318.13



Scheme-1: Indole bearing chalcones synthesis



Scheme 2: pyrimidine derivatives synthesis from chalcones

R = **4a** : 4-OH; **4b** : 4-OCH_3; **4c** : 4-NH_2; **4d** : 4-Cl; **4e** : 4-Br; **4f** : 3-NO_2

4c: 4-(4-aminophenyl)-6-(1*H*-indol-3-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3667.72 (pyrimidine-OH str.), 3553.42, 3523.38 (primary amine -NH- str.), 3395.11 (indole -NH- str.), 3071.14 (aromatic =C-H str.), 1514.94 (aromatic C=C str.), 1603.62 (C=N str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 6.17 (2H, s, -N<u>H</u>$_2$), 7.83 (1H, s, pyrimidine-O<u>H</u>), 12.06 (1H, s, indole-N<u>H</u>-), 6.58-6.69 (2H, d, phenyl-C_2-H & C_6-H), 7.54-7.67 (2H, d, phenyl-C_3-H & C_5-H), 7.94 (1H, s, pyrimidine-C_5-H), 7.25-8.60 (5H, m, indole-Ar-H). ESI-MS: m/z (M^+) 303.14

4d: 4-(4-chlorophenyl)-6-(1*H*-indol-3-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3639.66 (pyrimidine-OH str.), 3450.31 (indole -NH- str.), 3067.11 (aromatic =C-H str.), 1515.02 (aromatic C=C str.), 1644.92 (C=N str.), 698.37 (C-Cl str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 7.81 (1H, s, pyrimidine-O<u>H</u>), 11.69 (1H, s, indole-N<u>H</u>-), 7.54-7.62 (2H, d, phenyl-C_2-H & C_6-H), 7.98-8.09 (2H, d, phenyl-C_3-H & C_5-H), 7.69 (1H, s, pyrimidine-C_5-H), 7.10-8.71 (5H, m, indole-Ar-H). ESI-MS: m/z (M^+) 321.09

4e: 4-(4-bromophenyl)-6-(1*H*-indol-3-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3612.49 (pyrimidine-OH str.), 3331.28 (indole -NH- str.), 3071.77 (aromatic =C-H str.), 1515.03 (aromatic C=C str.), 1602.77 (C=N str.), 544.31 (C-Br str.).

^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 7.73 (1H, s, pyrimidine-OH), 11.91 (1H, s, indole-NH-), 7.43-7.52 (2H, d, phenyl-C_2-H & C_6-H), 7.84-7.92 (2H, d, phenyl-C_3-H & C_5-H), 7.66 (1H, s, pyrimidine-C_5-H), 7.18-8.82 (5H, m, indole-Ar-H). ESI-MS: m/z (M^+) 365.02

4f: 4-(3-nitrophenyl)-6-(1*H*-indol-3-yl)-pyrimidin-2-ol

IR [KBr ν cm^{-1}]: 3613.30 (pyrimidine-OH str.), 3395.50 (indole -NH- str.), 3066.36 (aromatic =C-H str.), 1514.26 & 1370.13 (nitro N-O str.), 1603.45 (aromatic C=C str.), 1690.26 (C=N str.). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d_6]: 7.74 (1H, s, pyrimidine-OH), 11.52 (1H, s, indole-NH-), 8.65 (1H, s, phenyl-C_2-H), 8.22-8.32 (1H, d, phenyl-C_4-H), 7.76-7.90 (1H, t, phenyl-C_5-H), 8.17-8.28 (1H, d, phenyl-C_6-H), 7.68 (1H, s, pyrimidine-C_5-H), 7.24-8.72 (5H, m, indole-Ar-H). ESI-MS: m/z (M^+) 332.07

Molecular Docking Studies

Molecular docking experiments were performed to predict molecular mechanisms at SARS Cov-2 main protease, cyclooxygenase-1 (COX-1) and cyclooxygenas-2 (COX-2) target proteins as potential anti-inflammatory agents. The 3D crystal structures cyclooxegenase-1 PDB ID: 3KK6[14-19] and cyclooxegenase-2 PDB ID: 5IKR[20-24] are downloaded in PDB format from RCBS protein data bank (https://www.rcsb.org/). The retrieved proteins were prepared for docking by removal of water molecules and heteroatoms using BIOVIA Discovery studio visualizer 2021. The proteins structures were minimized to least energy state by addind Kollman charges, Gasteiger charges and polar hydrogens for further analysis. The designed and synthesized ligand structures were drawn using ChemDraw Ultra 12.0, the structures was minimized and saved in SDF file format using Chem 3D-Pro 12.0 version. The standard ligand structure SDF file formats of Diclofenac (Pubchem Id: 3033) were downloaded from PubChem database. Further all the SDF format files are converted into PDB format using Open Babel software. Grid-based docking studies carried out using default parameters, protein transformations and other ligand molecules from PDB to PDBQT file format was done and docking was performed by linking the protein–ligand using MGL Autodock Vina. The docking poses of ligand with best linking at active site regions of the proteins were observed by using command prompt. The two-dimensional and three-dimensional bindings of the ligands with the target proteins were visualized using BIOVIA Discovery Studio 2021.

RESULTS AND DISCUSSION

According to the literature procedures, initially indole bearing chalcones (**3a-3f**) were synthesized by the Claisen-Schmidt reaction of substituted acetophenones and indole-3-aldehyde. Further, indole bearing chalcones treated with urea undergoes cyclization to afford indole bearing pyrimidin-2-ol derivatives (**4a-4f**). The scheme of synthesis of chalcones and titled pyrimidine derivatives was depicted in **Schme-1** and **Scheme-2** respectively. The physical characterization data was shown in **Table-1**.

Table-1: Physical characterization data of pyrimidine derivatives **4a-4f** & **5a-5f**							
Compd.	**R**	**m.p. (°C)**	**Molecular formula**	**mol.wt.**	**% yield**	**reaction time**	**R_f value**
4a	4-hydroxy	168-170	$C_{18}H_{13}N_3O_2$	303.31	72.61	15.5 hrs	0.52
4b	4-methoxy	146-148	$C_{19}H_{15}N_3O_2$	318.32	68.52	16 hrs	0.63
4c	4-amino	178-180	$C_{18}H_{14}N_4O$	303.33	70.38	15 hrs	0.58
4d	4-chloro	152-154	$C_{18}H_{12}N_3OCl$	321.29	66.47	17.5 hrs	0.50
4e	4-bromo	178-180	$C_{18}H_{12}N_3OBr$	365.12	62.12	18 hrs	0.62
4f	3-nitro	158-160	$C_{18}H_{12}N_4O_3$	332.17	76.20	15.5 hrs	0.56

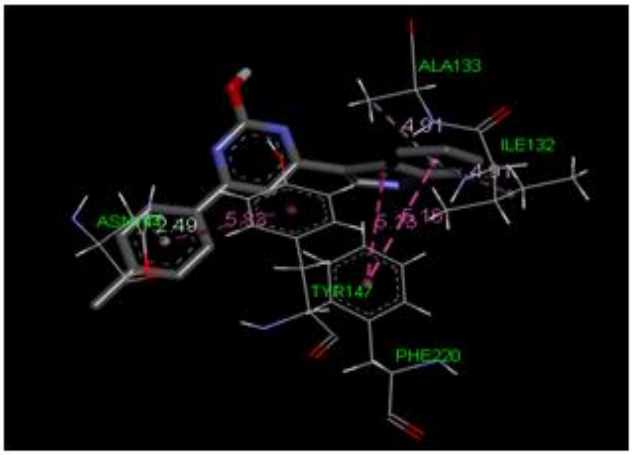
Molecular docking results

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

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

Designed ligands were screened at active site region of cyclooxegenase-1 (3KK6) in comparison with standard ligand Diclofenac. Screening results for cyclooxegenase-1 protein 3KK6 with designed ligands and standard ligand Diclofenac were shown in **Table-2**, **Figure-1,** and **Figure-2**. Docking energy of the interacted standard ligand Diclofenac at the active site region −4.13 kcal/mol was found to be less as compared to that of designed ligands **4d** docking energy −4.99 kcal/mol, indicating that significant more likely ligands at cyclooxegenase-1 protein.

Table-2: Binding energy & amino acid residues interacted with COX-1 protein target PDB ID – 3KK6.		
Compound	**Binding energy (kcal/mol)**	**Interacted amino acid residues**
Diclofenac	-4.13	Ala133, Phe220, Ile132
4a	-2.17	Leu253, His21, Cys285, Met265
4b	-3.25	Gly284, Arg189, Ile320
4c	-3.10	Leu252, Cys138, Met247, Ser242
4d	-4.99	Tyr147, Asn144, Ala133, Ile132, Phe220
4e	-3.59	Gly140, Cys255, Tyr273, Arg260
4f	-3.18	Ile241, Leu168, Arg189, Ala220



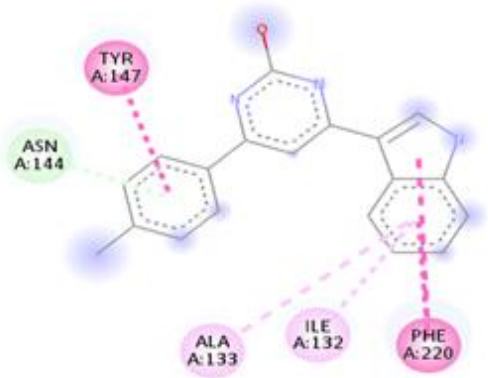


Figure-1: Three-dimensional & two-dimensional binding mode of designed ligand compounds **4d** at active site region of cyclooxegenase-1 protein PDB ID- 3KK6

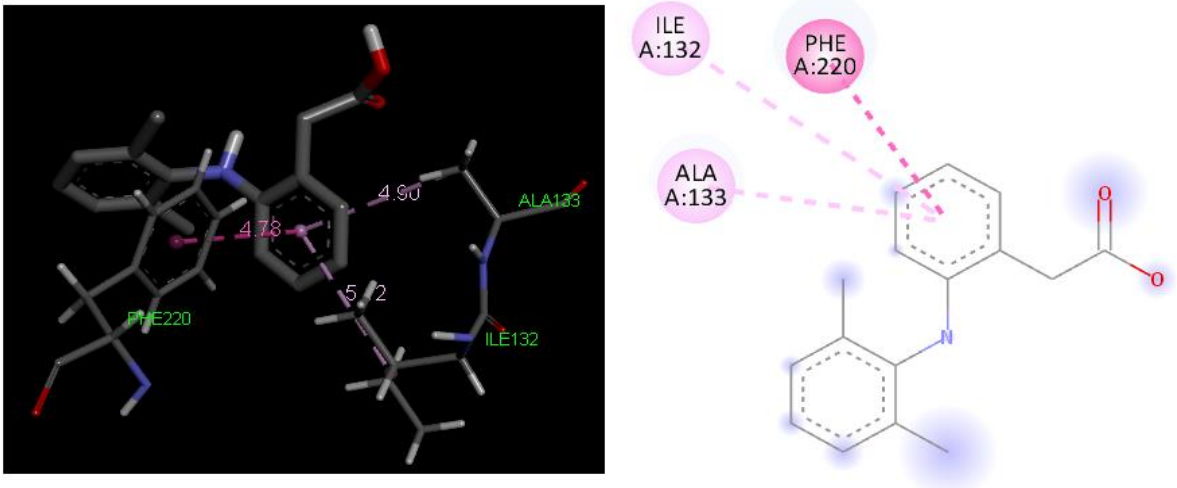


Figure-2: Three-dimensional & two-dimensional binding mode of standard ligand Diclofenac at active site region of cyclooxegenase-1 protein PDB ID- 3KK6

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

Designed ligand was screened at active site region of cyclooxegenase-2 (5IKR) in comparison with standard ligand Diclofenac. Screening results for cyclooxegenase-2 protein 5IKR with designed ligand and standard ligand Diclofenac were shown in **Table-3, Figure-3,** and **Figure-4**. Docking energy of the interacted standard ligand Diclofenac at the active site region −4.27 kcal/mol was found to be less as compared to that of designed ligands **4d** docking energy −5.48 kcal/mol, indicating that significant more likely ligands at cyclooxegenase-2 protein.

Table-3: Binding energy & amino acid residues interacted with COX-2 protein target PDB ID – 5IKR.

Compound	**Binding energy (kcal/mol)**	**Interacted amino acid residues**
Diclofenac	-4.27	Ala132, Gly217, Pro218, Asp133, Ala219
4a	-3.89	Ile244, Val165, His215, Ser253
4b	-3.64	Ala327, Ser320, Val223, Leu198
4c	-3.75	Leu252, Arg310, Ser324, Tyr280
4d	-5.48	Tyr147, Asn144, Arg216
4e	-2.97	Ser220, Gln241, Arg188, Val219
4f	-3.55	His180, Arg220, Ser300, Cys184

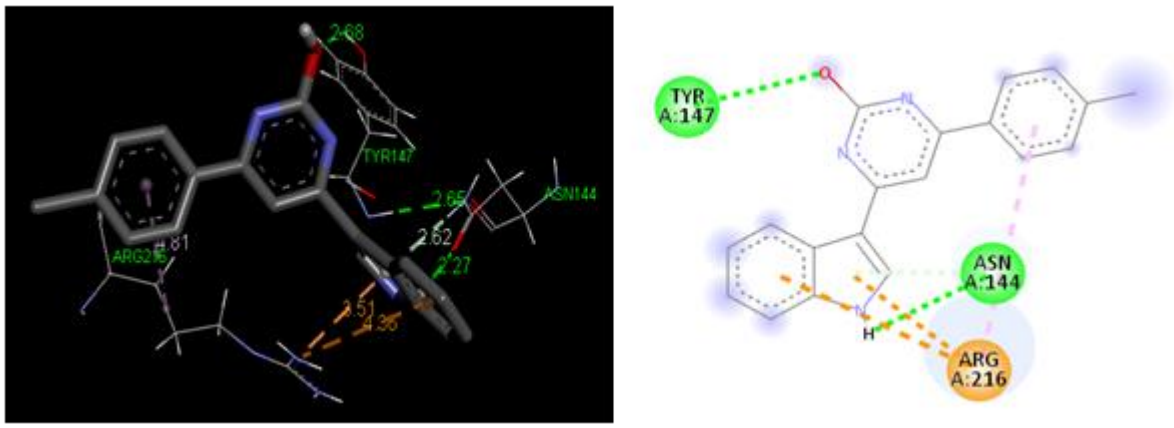


Figure-3: Three-dimensional & two-dimensional binding mode of designed ligand compounds **4d** at active site region of cyclooxegenase-2 protein PDB ID- 5IKR

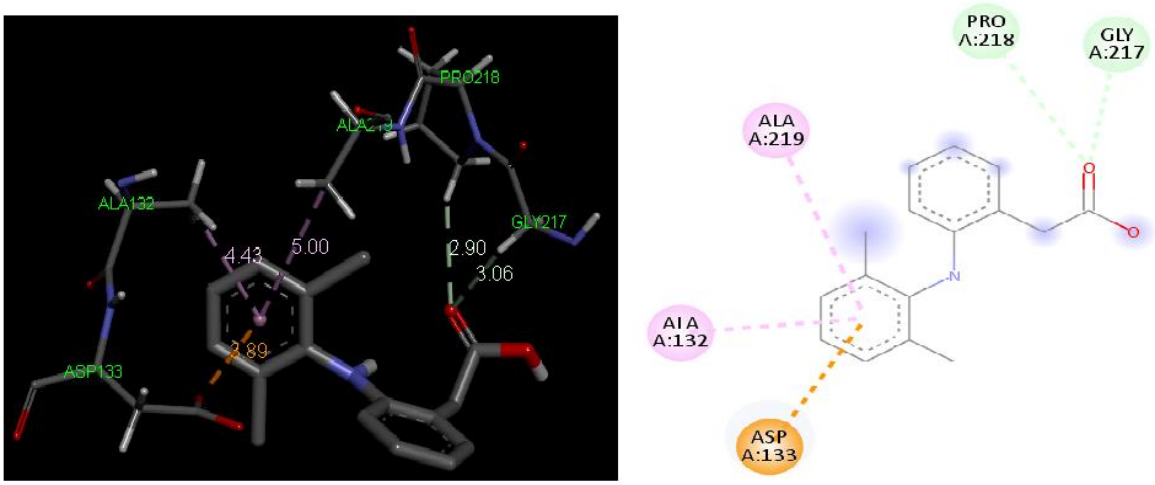


Figure-4: Three-dimensional & two-dimensional binding mode of standard ligand Diclofenac at active site region of cyclooxegenase-2 protein PDB ID- 5IKR

CONCLUSION

In this investigation, titled compounds of various novel pyrimidine derivatives **4a-4f** bearing indole moiety were designed and synthesized. Characterization of the compounds was done by physically and spectrally. All the compounds were computationally screened through molecular docking studies at COX-1 (PDB ID-3KK6) and COX-2 (PDB ID-5IKR) receptor proteins. Among the entire developed compounds **4d** exhibit significant binding affinity when compared with standard ligand Diclofenac, suggesting that 4-(4-chlorophenyl)-6-(1*H*-indol-3-yl)-pyrimidin-2-ol is lead compound for developing effective and safe anti-inflammatory agents.

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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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