INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Paper

# Construction of Novel Triazolothione, Thiadiazole, Triazole Functionalized Quinoline Derivatives; Their Biological Evolutions and Docking Interactions

**Chakravarthy Bhupathi[1], Raghu Dasari[2], Kavitha Tula[3], Shravan Kumar Gunda[4], Namratha Vaddiraju*[5]**

[1,2,3,5] *Department of chemistry, Satavahana University, Karimnagar, Telangana, INDIA, 505001*
[4]*Bioinformatics Division, PGRRCDE, Osmania University, Hyderabad, Telangana-500007, INDIA.*

ARTICLE INFO

Published: 21 July 2026
Keywords:
Quinoline, Triazolothione, Thiadiazole, Triazole, Anticancer activity, Antimicrobial activity, Anti-inflammatory activity, Molecular docking interactions
DOI:
10.5281/zenodo.21470978

## ABSTRACT

Construction of triazolothione, thiadiazole, triazole-functionalized quinoline derivatives 5a-d, 6a-d and 7a-d respectively, were prepared starting from 6-fluoro-2-(trifluoromethyl)quinolin-4-ol 1 through reaction with bromoethyl acetate to afford selective O-alkylation derivative 2, followed by reaction with hydrazine hydrate resulted carbohydrazide derivatives 3 and further reacted with diverse substituted phenyl isothiocyanates to form quinoline hydrazine carbothiamide derivatives 4a-d. Each compound is independently reacted in presence of NaOH, H2SO4, and N2H4.H2O to form triazolothione, thiadiazole, triazole-functionalized quinoline derivatives 5a-d, 6a-d and 7a-d respectively. All the products 5a-d, 6a-d and 7a-d were screened against anticancer activity on four human cancer cell lines HeLa (cervical cancer, CCL-2), COLO 205 (colon cancer, CCL-222), HepG2 (liver cancer, HB-8065), and MCF7 (breast cancer, HTB-22), using the MTT assay promising compounds 7b and 7c identified. All the products were screened anti-inflammatory activity, among the compounds tested, the compounds 5a, 5b, 5d and 6a exhibited significant inhibition of IL-1b secretion as a measure of anti-inflammatory activity

## INTRODUCTION

Quinoline is a bicyclic aromatic heterocycle containing a single nitrogen atom. It is widely found in numerous natural products as well as many clinically used drugs, which has established its significance in drug discovery. The quinoline core is present in a variety of therapeutically important agents, including antibiotics [1], anticancer [2], antiviral [3], antimalarial [4], and

***Corresponding Author:** Namratha Vaddiraju
**Address:** *Assistant Professor, Department of chemistry, Satavahana University, Karimnagar-505001, TS-India..*
**Email** ✉: namrathav69@gmail.com
**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

antitubercular [5] drugs. Notable examples include Levofloxacin, Foretinib, Cabozantinib, Neratinib, Saquinavir, Primaquine, and Bedaquiline.

In drug discovery, the strategy of combining two or more pharmacophores into a single molecular framework to achieve enhanced or dual biological activity compared to the parent compounds is known as hybridization [6]. Hybrid molecules often help address limitations associated with conventional drugs, such as poor bioavailability, drug resistance, toxicity, and adverse side effects. Owing to these advantages, hybrid drugs have attracted significant attention in medicinal chemistry. Numerous review articles have reported on the synthesis and biological applications of quinoline derivatives [7–9], and green synthetic approaches for quinoline derivatives have also been extensively reviewed [10].

Moreover, the quinoline ring system is widely present in many natural products, particularly alkaloids, and serves as an important framework in the design of numerous synthetic compounds with diverse pharmacological activities. Several quinoline-based natural products are used directly as therapeutic agents or act as lead molecules for the development of more potent analogues. For instance, quinine (Structure 1), isolated from the bark of *Cinchona* trees, has long been used in the treatment of malaria. Its structural elucidation and structure–activity relationship (SAR) studies led to the development of improved antimalarial drugs such as chloroquine (Structure 2), primaquine (Structure 3), and mefloquine (Structure 4) [11]. Chimanine alkaloids and simple quinoline derivatives (Structures 5–6), obtained from the bark of *Galipea longiflora* (Rutaceae family), exhibit activity against *Leishmania* species, the causative agents of leishmaniasis [12]. Cryptolepine (Structure 7), an indoloquinoline alkaloid, is found in the West African shrub *Cryptolepis sanguinolenta* [13]. Additionally, dynemicin A (Structure 8) is naturally occurring quinoline-containing antitumor antibiotics [14,15,16].

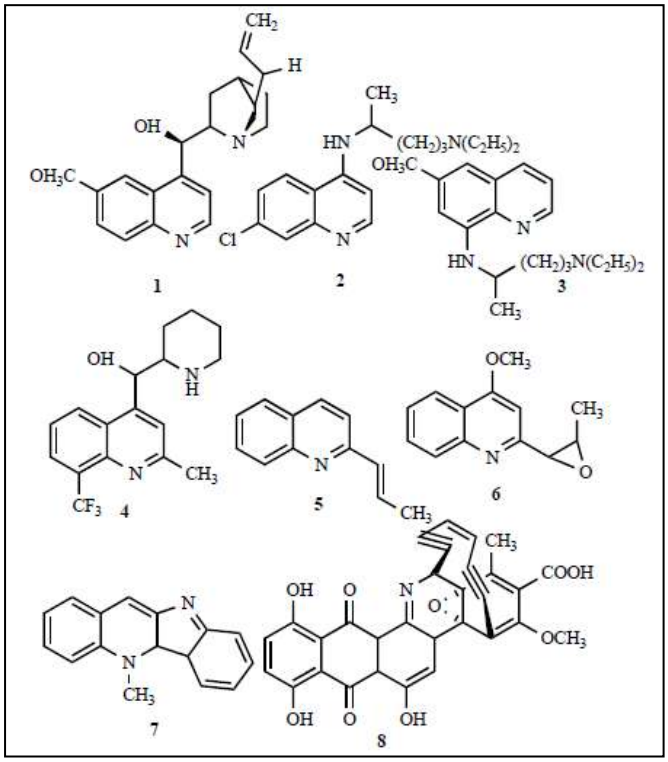


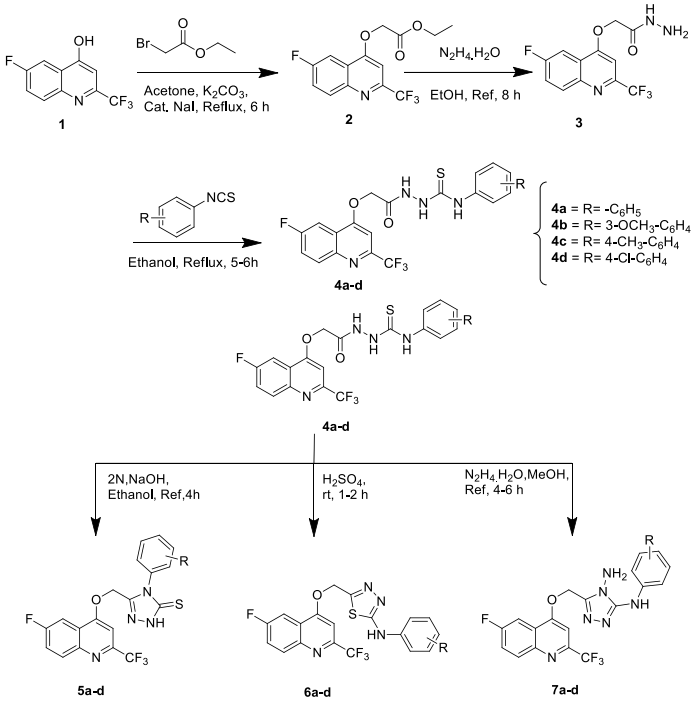

**Figure 1: Bioactive compounds based on quinoline**

The incorporation of trifluoromethyl group/fluoro group [17-23] at specific positions within organic molecules can lead to significant enhance in their properties, such as increased lipid solubility, greater oxidative thermal stability, enhanced membrane permeability, and increased oral bioavailability.

To continue our research efforts[24-29], in our research program we designed and synthesized novel triazolothione, thiadiazole, triazole functionalized quinoline derivatives and evaluated for their anticancer and anti-inflammatory activities, and promising compounds which showed good activity have been identified and further evaluated for docking interactions.

## CHEMISTRY:

Compound 6-fluoro-2-(trifluoromethyl)quinolin-4-ol **1** on reaction with bromoethyl acetate in the presence of $K_2CO_3$ and cat. amount of NaI in acetone as solvent for about 6h refluxing condition to get ethyl 2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetate **2.** Further compound **2** reaction with hydrazine hydrate in ethanol refluxing condition and obtained 2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetohydrazide **3**. Reaction between Compound **3** and diverse substituted isothiocyanatobenzene in ethanol refluxing condition to obtain 2-(2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetyl)-N-phenyl hydrazine carbothioamide **4a-d**. Each compound **4a-d** is independently reacted in presence of NaOH in ethanol, $H_2SO_4$, and $N_2H_4.H_2O$ in methanol to form triazolothione, thiadiazole, triazole-functionalized quinoline derivatives **5a-d, 6a-d** and **7a-d** respectively. Reaction details were outlined in scheme.




1 2 3 4a-d 4a-d 5a-d 6a-d 7a-d

5a=R=$C_6H_5$ 6a=R=$C_6H_5$ 7a=R=$C_6H_5$
5b=R=3-$OCH_3$-$C_6H_4$ 6b=R=3-$OCH_3$-$C_6H_4$ 7b=R=3-$OCH_3$-$C_6H_4$
5c=R=4$CH_3$-$C_6H_4$ 6c=R=4$CH_3$-$C_6H_4$ 7c=R=4$CH_3$-$C_6H_4$
5d=R=4Cl-$C_6H_4$ 6d=R=4Cl-$C_6H_4$ 7d=R=4Cl-$C_6H_4$

**Scheme**: **Synthesis of novel triazolothione, thiadiazole, triazole functionalized quinoline derivatives 5a-d, 6a-d and 7a-d.**

## RESULTS AND DISCUSSION:

### *Anticancer activity*

The synthesized compounds **5a-d**, **6a-d and 7a-d** were screened for their inhibitory activity against four human cancer cell lines: HeLa (cervical cancer, CCL-2), COLO 205 (colon cancer, CCL-222), HepG2 (liver cancer, HB-8065), and MCF7 (breast cancer, HTB-22), using the MTT assay [30]. 5-Fluorouracil was used as the standard control in the study. Most of the products showed promising cytotoxic activity across all the four cell lines, although some compounds displayed no significant response up to concentrations of 118.2 µM (Table 1).

Compounds **7b** and **7c**, which contain 4-methoxyphenyl and 4-methl phenyl substituents, demonstrated superior activity to their analogs. This finding suggests these scaffolds are promising for drug development. Anticancer activity results were tabulated in table 1

**Table 1. In vitro cytotoxicity of compounds 5a-d, 6a-d and 7a-d.**

| Compound | $IC_{50}$ values (in µM) HeLa | COLO205 | HepG2 | MCF7 |
|---|---|---|---|---|
| **5a** | 29.80 ± 1.52 | 25.70 ± 1.28 | --- | 49.44 ± 3.25 |
| **5b** | 31.25 ± 0.21 | 34.50 ± 1.25 | 43.60 ± 0.22 | 63.30 ± 4.41 |
| **5c** | 45.10 ± 3.41 | --- | 24.20 ± 1.23 | 21.33 ± 0.13 |
| **5d** | --- | --- | --- | 118.2±0.38 |
| **6a** | 25.20 ± 1.68 | 42.52 ± 3.49 | --- | --- |
| **6b** | --- | 55.76 ± 0.26 | --- | 96.80 ± 5.38 |
| **6c** | --- | 27.74 ± 0.12 | --- | --- |
| **6d** | 18.20 ± 0.32 | --- | --- | --- |
| **7a** | 22.23 ± 0.37 | 12.3 ± 0.20 | 32.2 ± 1.37 | |
| **7b** | 18.50 ± 0.22 | 9.21 ± 0.37 | 7.10 ± 0.20 | 14.40 ± 0.22 |
| **7c** | 13.26 ± 0.62 | --- | 19.50 ± 0.42 | 10.42 ± 0.28 |
| **7d** | --- | 32.30 ± 0.26 | --- | 71.42 ± 0.28 |
| **5-Fluorouracil** (Std control) | 1.8 ± 0.09 | 1.9 ± 0.11 | 1.7±0.08 | 1.8±0.07 |

---indicates $IC_{50}$ value >118.2 µg/mL, Cell lines used: HeLa - Cervical cancer (CCL-2), COLO 205- Colon cancer (CCL-222), HepG2- Liver cancer (HB-8065), MCF7 - Breast cancer (HTB-22),

### *Anti-inflammatory activity*

All final compounds (**5a–d, 6a–d**, and **7a–d**) were evaluated for their anti-inflammatory activity using a PMA (phorbol 13-myristate 12-acetate)-induced inflammation model in THP-1 monocyte cells. Among the tested compounds, **5a**, **5b**, **5d** and **6a** demonstrated significant inhibition of IL-1β secretion, indicating notable anti-inflammatory potential, with $IC_{50}$ values ranging from 5.9 to 9.6 mM (see Table 5). Under identical experimental conditions, piroxicam, a well-known COX-2 inhibitor, exhibited an $IC_{50}$ value of 18 mM. Furthermore, none of the compounds showed any effect on cell viability, even at a concentration of 20 mM (data not shown), confirming that their anti-inflammatory activity is not associated with cytotoxic effects. Structure–activity relationship (SAR) analysis suggested that the triazolothione quinoline derivatives observed more prominent activity. Further investigations are in progress to optimize the lead compounds. Activity results were tabulated in table 2.

**Table 2:**IL-1β secretion inhibition efficacy (as a measure of anti-inflammatory activity) of the synthesized compounds **5a-d**, **6a-d** and **7a-d**.[a]

| S. No | Compounds | IL-1β (IC50 mM)[b] |
|---|---|---|
| 1 | **5a** | 7.2 ± 1.8 |
| 2 | **5b** | 9.6 ± 3.4 |
| 3 | **5c** | NA |
| 4 | **5d** | 5.9 ± 2.1 |
| 5 | **6a** | 6.2 ± 2.4 |
| 6 | **6b** | 11.8 ± 1.4 |
| 7 | **6c** | NA |
| 8 | **6d** | 20.0 ± 1.6 |
| 9 | **7a** | NA |
| 10 | **7b** | 14.9 ± 3.2 |
| 11 | **7c** | NA |
| 12 | **7d** | 16.4 ± 2.8 |
| 13 | **Piroxicam**[c] | 18.0 ± 2.7 |

[a]THP1 monocytes were pre-treated with 5, 10 and 20 mM concentrations of the above mentioned Quinoline derivatives **5a-d**, **6a-d** and **7a-d** for 2 h before simulation with 100 nM Phorbol 13-myristate 12-acetate (PMA) to induce inflammation for a period of 48 h. At the end of the treatment, conditioned media was collected and the level of IL-1β was measured by ELISA as described in the experimental section.

[b]IC50 values are mean ± SD of three independent experiments, NA: indicates IC50 value >20 mM.

[c]Piroxicam, a known anti-inflammatory agent was used as a positive control

**Anti-inflammatory activity**

All final compounds (**5a–d, 6a–d,** and **7a–d**) were evaluated for their anti-inflammatory activity using a PMA (phorbol 13-myristate 12-acetate)-induced inflammation model in THP-1 monocyte cells.[31] Among the tested compounds, **5a**, **5b**, **5d** and **6a** demonstrated significant inhibition of IL-1β secretion, indicating notable anti-inflammatory potential, with $IC_{50}$ values ranging from 5.9 to 9.6 mM (see Table 2). Under identical experimental conditions, piroxicam, a well-known COX-2 inhibitor, exhibited an $IC_{50}$ value of 18 mM. Furthermore, none of the compounds showed any effect on cell viability, even at a concentration of 20 mM (data not shown), confirming that their anti-inflammatory activity is not associated with cytotoxic effects. Structure–activity relationship (SAR) analysis suggested that the triazolothione quinoline derivatives observed more prominent activity. Further investigations are in progress to optimize the lead compounds.

## MATERIALS AND METHODS:

The in-silico molecular docking study was carried out for the two synthesized compounds and one control drug i.e., Piroxicam by using the Autodock 4.2. Ligand, protein preparation, grid generation and receptor-ligand docking were carried out by using Autodock4.2 software.[32].

**Selection and preparation of target protein:**

The Crystal "HUMAN INTERLEUKIN-1 BETA" whose PDB ID is 9ILB[33], was retrieved from the PDB (Protein Data Bank) and used for molecular docking. It seems to have a 2.28 Å resolution and one 153 aminoacid residues of protein chain A. The molecular weight of the protein is 17376.87 kDa.[34] AutoDockTools (ADT) 1.5.6 was used to prepare the input files and removed water molecules. Added all hydrogen's and saved it in PDBQT format.

**Selection and Preparation of ligand molecules:**

The molecules were sketched and energy minimized by using *Gasteiger-Hückel charges in sybyl6.7 software and saved it in .mol2 format.*[35] The ligands being uploaded individually in .mol2 format into the AutoDockTools, root was selected and saved it in PDBQT format.

***Molecular docking Analysis:***

AutoDock 4.2 was performed to validate the binding efficacy of the protein-ligand complex. Molecular docking analysis was performed using Autodock 4.2 tool. The protein 9ILB and ligand was uploaded individually and removed water molecules and added all Hydrogens. Later the protein was saved in pdbqt format. Autodock uses Genetic Algorithm. The standard docking procedure was employed for a rigid protein and a flexible ligand whose torsion angles were identified. Grid dimensions selected as 60, 60, and 60 points and the amino acids which are present in the active site were selected and centered the in x, y, and z directions was built with a grid spacing of 0.375 Å and a distance-dependent function of the dielectric constant were used for the calculation of the energetic map[36]. The default settings were used for all other parameters[37]. Lamarckian genetic algorithm method was employed for docking simulations. The default settings were used for all other parameters. At the end of docking, the best poses were analyzed for hydrogen bonding calculations using Autodock 4.2, Ligplot plus[38] and Biovia Discovery studio visualizer[39]. Estimated ΔGbinding, kcal/mol (free energy of ligand binding), the Ki (inhibition constant) for each compound was calculated.

**Docking Interactions:**

The docking analysis was performed for two synthesized and the control Piroxicam compounds against the Crystal Structure of HUMAN INTERLEUKIN-1 BETA, represented by the crystal structure 9ILB, at a resolution of 2.28 Å, which provides a reliable structural framework for evaluating ligand interactions.

The molecular docking results revealed notable differences in binding affinities and interaction profiles among the tested compounds, including the reference drug Piroxicam.

Compound 1 exhibited a most negative binding affinity of **−5.00 kcal/mol**, interacting with residues **Val41, Lys63, and Lys65**. Similarly, Compound 2 showed a slightly improved binding affinity of **−5.53 kcal/mol**, with interacting **Gln39, Val41, Lys63, and Lys65**. The additional interaction with Gln39 in Compound 2 may account for its marginally better binding energy compared to Compound 1, suggesting improved stabilization within the binding pocket.

In contrast, **Piroxicam** demonstrated a significantly stronger binding affinity of **−7.63 kcal/mol**, interacting with **Met20, Glu37, Gln39, and Val41**. The more favorable binding energy indicates a stronger and more stable ligand–protein complex. This enhanced interaction may be attributed to the involvement of key residues such as Glu37 and Met20, which are not engaged by the test compounds. These residues could play a critical role in ligand stabilization, possibly through hydrogen bonding, electrostatic interactions, or hydrophobic contacts.

A comparative analysis highlights that **Val41** is a common interacting residue across all ligands, suggesting its importance in the binding pocket architecture. Additionally, **Gln39** appears in both Compound 2 and Piroxicam interactions, indicating its potential contribution to improved binding affinity when involved.

Despite showing interactions with key residues like Lys63 and Lys65, Compounds 1 and 2 displayed weaker binding affinities compared to Piroxicam. This suggests that their interaction profiles may lack the optimal combination of contacts required for strong binding, particularly

with residues such as Glu37 and Met20. Furthermore, the absence of interactions with these critical residues may limit their overall inhibitory potential.

Overall, while Compound 2 demonstrates slightly better binding than Compound 1, both compounds exhibit lower binding affinity compared to Piroxicam. These findings suggest that although the tested compounds can occupy the active site and interact with important residues, further structural optimization is necessary to enhance their binding strength and mimic the interaction pattern of the standard drug.

| Compound number | Binding energy ΔG (kcal/mol) | Dissociation constant (kl) | Interacting amino acids |
|---|---|---|---|
| 5d | -5.00 | 215.71 µM | Val41, Lys63, Lys65 |
| 6a | -5.53 | 89.11 µM | Gln39, Val41, Lys63, Lys65 |
| Piroxicam | -7.63 | 2.57 µM | Met20, Glu37, Gln39, Val41 |

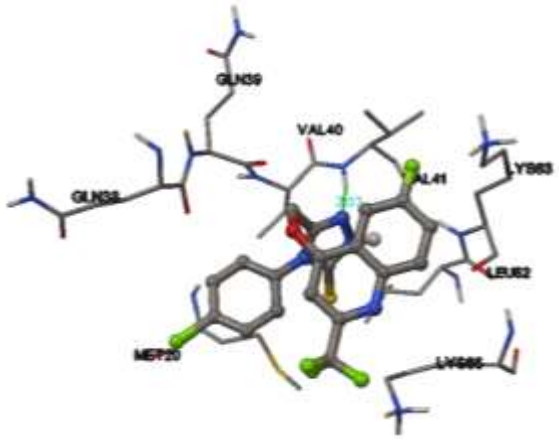



**Fig. 2. 3-Dimensional representation of compound 5d against human interleukin 1beta target (9ILB)**

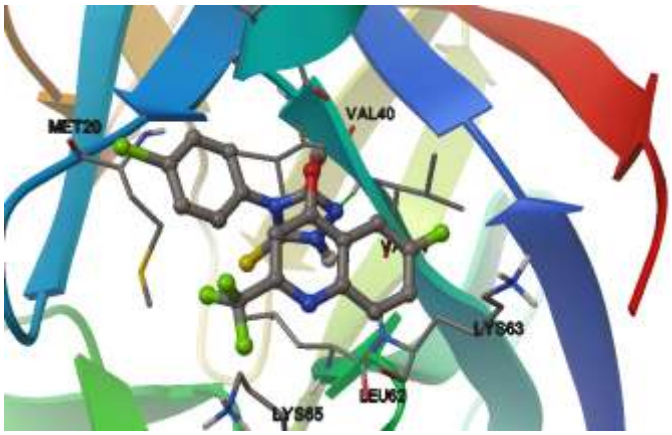



**Fig.3. 3D-with secondary structure docking confirmation of compound 5d against human interleukin 1beta target (9ILB)**

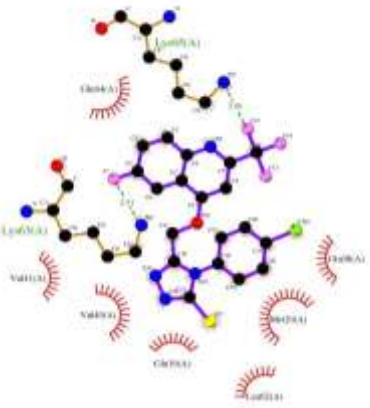


**Fig.4. 2D-docking and Ligplot docking confirmation of compound 8d against human interleukin 1beta target (9ILB)**

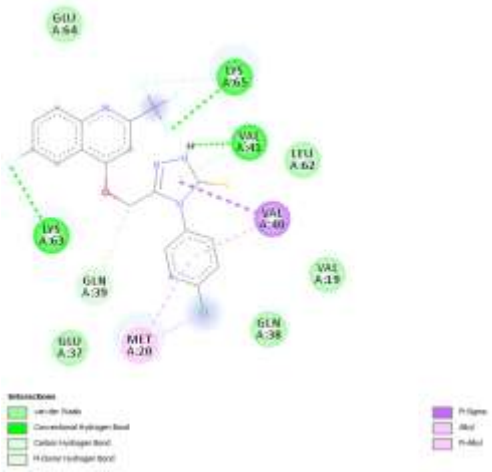



**Fig.5. 2D-docking confirmation of ligand 5d against human interleukin 1beta target (9ILB)**

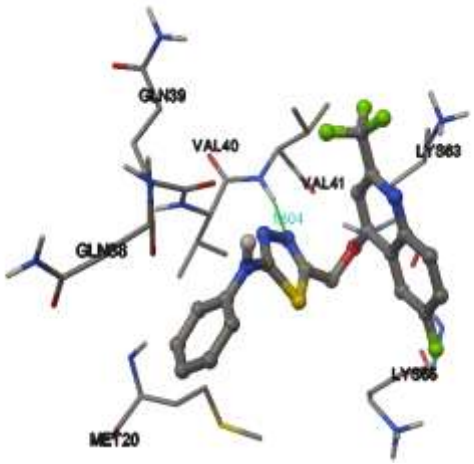



**Fig.6. 3-Dimensional representation of compound 6a against human interleukin 1beta target (9ILB)**

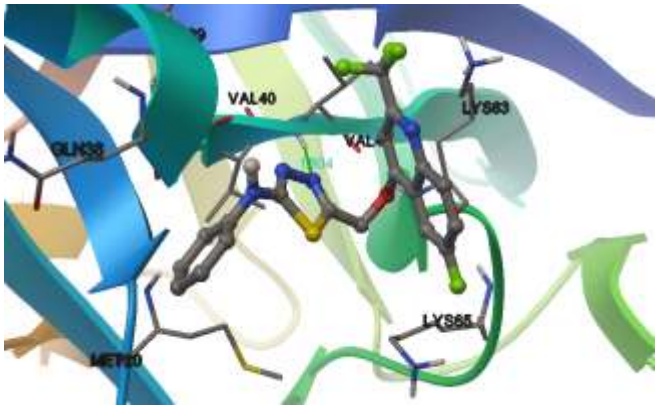



**Fig.7. 3D-with secondary structure docking confirmation of compound 6a against human interleukin 1beta target (9ILB)**

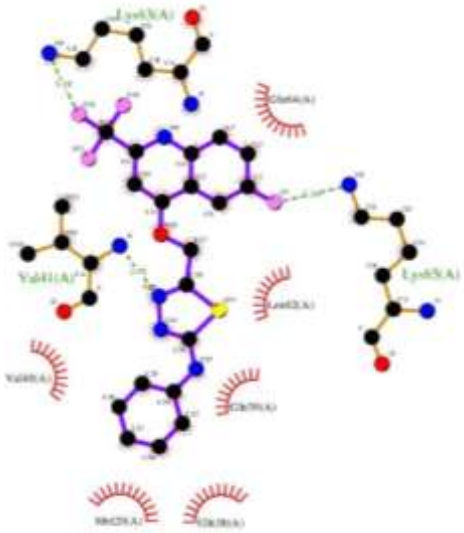


**Fig.8. 2D-docking and Ligplot docking confirmation of compound 6a against human interleukin 1beta target (9ILB)**

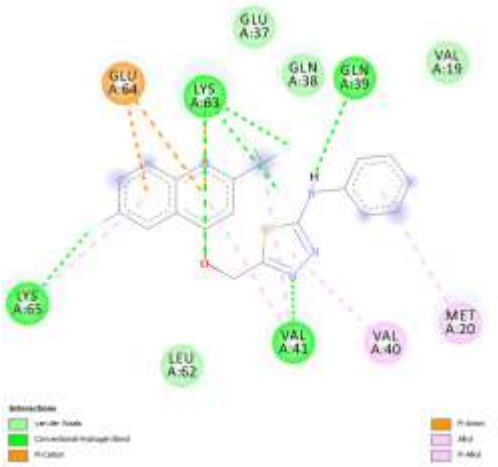



**Fig.9. 2D-docking confirmation of ligand 6a against human interleukin 1beta target (9ILB)**

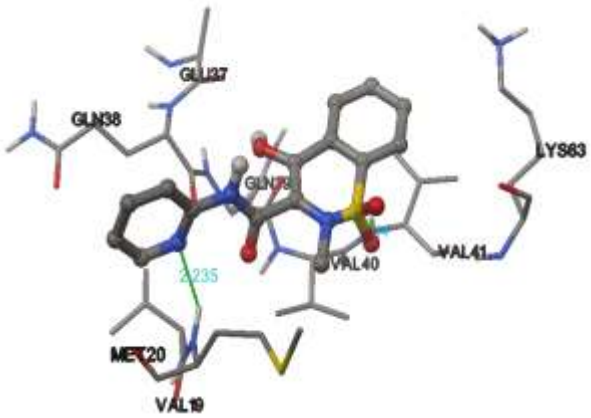
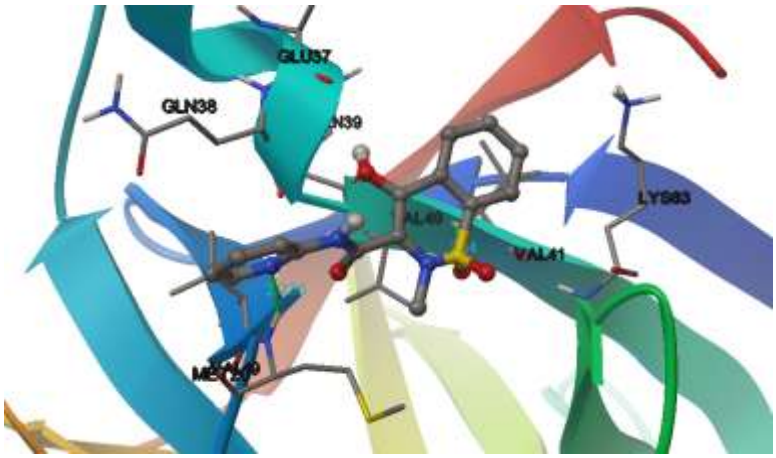



**Fig.10. 3-Dimensional representation of compound Piroxicam against human interleukin 1beta target (9ILB)**




.

**Fig.11. 3D-with secondary structure docking confirmation of compound Piroxicam against human interleukin 1beta target (9ILB)**

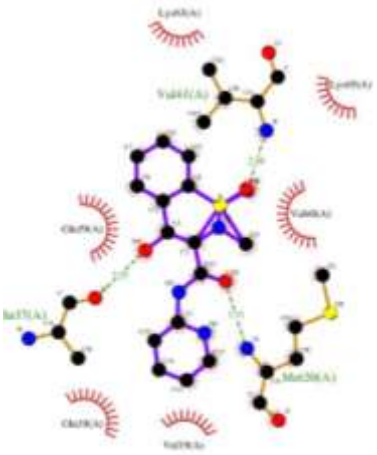


**Fig.12. 2D-docking and Ligplot docking confirmation of compound Piroxicam against human interleukin 1beta target (9ILB)**

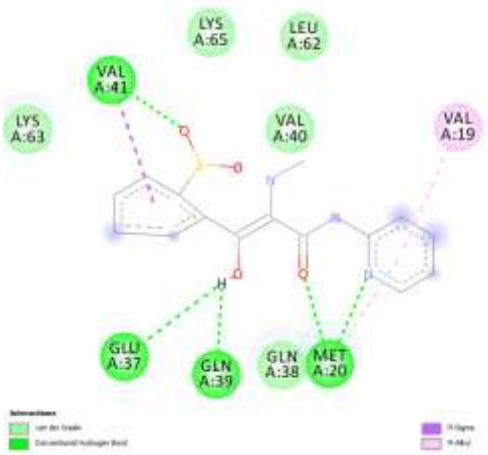



**Fig.13. 2D-docking confirmation of ligand Piroxicam against human interleukin 1beta target (9ILB)**

***General procedure for the preparation of ethyl 2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetate (2)***

Charged Compound 6-fluoro-2-(trifluoromethyl)quinolin-4-ol **1,** bromoethylacetate, $K_2CO_3$ and cat. amount of NaI in acetone. The reaction mixture was refluxed for 6-8 h and after cooling to room temperature the acetone was removed under vacuum. The residue was washed with n-hexane and then water was added to give a grey solid which was filtered with water and dried. Grey solid; Yield 71%; $^1$H NMR ($CDCl_3$, 300 MHz): δ 1.27 t (3H, -$CH_3$), 4.23 q (2H, -$CH_2$), 4.68 s (2H, -$OCH_2$), 7.10 s (1H, Ar-H), 7.44 dd (*J*=7.6 Hz, 1H, Ar-H), 7.62 dd (*J*=7.6 Hz, 1H, Ar-H), 8.05 m (1H, Ar-H); MS (ESI): *m/z* [$(M+H)^+$]: Found, 318. Calcd, 317; Anal. calc. for $C_{14}H_{11}F_4NO_3$: C 53.00; H 3.49; N 4.42 %. Found: C 53.02; H 3.51; N 4.45%.

***Preparation of 2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetohydrazide (3)***

Ethyl 2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetate **2** on reaction hdrazine hydrate in the presence of ethanol refluxing condition for about 6-8 hours, and after confirmation of the product by TLC, reaction mixture was allowed to cool and obtained 2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetohydrazide **3** by filtration. Grey solid; Yield 71%; $^1$H NMR ($CDCl_3$, 300 MHz): *δ* 4.52 (br. s., 2H, -$NH_2$), 4.72 s (2H, -$OCH_2$), 7.12 (s, 1H, Ar-H), 7.49 (dd, *J*=7.9 Hz, 1H, Ar-H), 7.65 (d, *J*=7.9 Hz, 1H, Ar-H), 8.09 (m, 1H, Ar-H), 9.28 (br. s., 1H, -CONH-); MS (ESI): m/z [$(M+H)^+$]: 304; Anal. calc. for $C_{12}H_9F_4N_3O_2$: C 47.53, H 2.99, N 13.86 %. Found: C 47.55, H 2.98, N 13.88 %.

***General procedure for the preparation of 2-(2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetyl)-N-phenylhydrazinecarbothioamide (4a-d)***

The 2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)acetohydrazide **3** (2 mmol) was taken in 95% ethanol (20 ml) and phenylisothiocyanate (2 mmol) was added, the reaction mixture was refluxed for 5-6 hrs and after cooling to room temperature the ethanol was removed under vacuum. The residue was washed with n-hexane and it gives light yellow solid and dried to get 2-(2-((6-fluoro-2-(trifluoromethyl) quinolin-4-yl)oxy)acetyl)-N-phenyl hydrazine carbothioamide. Grey solid; Yield 81%; 3522 (-NHCO-), 3375, 3310 (-$NH_2$), 1671 (-NHCO); $^1$H NMR (DMSO-$d_6$, 300 MHz): *δ* 4.81 (s, 2H, -$OCH_2$), 7.09 (s, 1H, Ar-H), 7.18 (dd, 1H, Ar-H), 7.26-7.32 (m, 3H, Ar-H), 7.41-7.45 (m, 2H, Ar-H), 7.60 (dd, 1H, Ar-H), 8.15 (m, 1H, Ar-H), 9.15 (br.

s, 1H, -NH-), 9.90 (br. s, 1H, -NH-), 10.84 (br. S, 1H, -NH-); MS (ESI): m/z [(M+H)$^+$]: 439; Anal. calc. for $C_{19}H_{14}F_4N_4O_2S$: C 52.05, H 3.22, N 12.78 %. Found: C 52.08, H 3.24, N 12.80 %.

**General procedure for the preparation of 3-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione derivatives (5a-d):**

A solution of 2-(2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl) oxy) acetyl)-N-phenyl hydrazine carbothioamide **4** (0.01 mol) in 2N NaOH was allowed to reflux for 2h. The resulting solution was cooled to room temperature and acidified to pH 3-4 with 37% hydrochloric acid. The precipitate formed was filtered and washed with distilled water, dried and crystallized to furnish the compound **5a-d**.

***3-(((6-Fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (5a)***. Yellow solid; Yield 75%; M.Pt. 185-187 °C; $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 4.81 (s, 2H, -OCH$_2$), 7.09 (s, 1H, Ar-H), 7.15 (dd, 1H, Ar-H), 7.26-7.32 (m, 3H, Ar-H), 7.41-7.45 (m, 2H, Ar-H), 7.67 (dd, 1H, Ar-H), 8.11 (m, 1H, Ar-H), 12.84 (br. s, 1H, -NHCS-); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 78.4, 120.5, 122.4, 123.1, 124.7, 125.3, 126.5, 128.6, 129.7, 130.4, 133.5, 135.8, 136.7, 142.3, 148.3, 162.1, 165.4; MS (ESI): m/z [(M+H)$^+$]: 421; Anal. calc. for $C_{19}H_{12}F_4N_4OS$: C 54.28, H 2.88, N 13.33 %. Found: C 54.30, H 2.86, N 13.35 %.

***3-(((6-Fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-4-(3-methoxyphenyl)-1H-1,2,4-triazole-5(4H)-thione (5b).*** Yellow solid; Yield 70 %; M.Pt. 195-197 °C; $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 3.82 (s, 3H, -OCH$_3$), 4.83 (s, 2H, -OCH$_2$), 7.10 (s, 1H, Ar-H), 7.19 (dd, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 7.42-7.47 (m, 3H, Ar-H), 7.65 (dd, 1H, Ar-H), 8.08 (m, 1H, Ar-H), 12.81 (br. s, 1H, -NHCS-); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 55.6, 78.2, 119.5, 121.4, 122.6, 123.5, 124.8, 125.6, 126.5, 127.4, 128.5, 129.8, 131.3, 133.6, 135.4, 136.8, 142.4, 148.3, 162.3, 165.5; MS (ESI): m/z [(M+H)$^+$]: 451; Anal. calc. for $C_{20}H_{14}F_4N_4O_2S$: C 53.33, H 3.13, N 12.44 %. Found: C 53.35, H 3.15, N 12.46 %.

***3-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-4-(p-tolyl)-1H-1,2,4-triazole-5(4H)-thione (5c).*** Yellow solid; Yield 68 %; M.Pt. 201-203 °C; $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 2.34 (s, 3H, -CH$_3$), 4.81 (s, 2H, -OCH$_2$), 7.08 (s, 1H, Ar-H), 7.17 (dd, 1H, Ar-H), 7.29 (d, *J*= 8.0 Hz, 2H, Ar-H), 7.63 (dd, 1H, Ar-H), 7.74 (d, *J*= 8.0 Hz, 2H, Ar-H), 8.10 (m, 1H, Ar-H), 12.84 (br. s, 1H, -NHCS-); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 21.6, 78.1, 120.4, 122.2, 123.6, 124.7, 125.4, 126.6, 127.3, 128.6, 129.7, 130.5, 133.4, 136.7, 142.3, 148.6, 162.4, 165.6; MS (ESI): m/z [(M+H)$^+$]: 435; Anal. calc. for $C_{20}H_{14}F_4N_4OS$: C 55.30, H 3.25, N 12.90 %. Found: C 55.32, H 3.28, N 12.89 %.

***4-(4-Chlorophenyl)-3-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-1H-1,2,4-triazole-5(4H)-thione (5d).*** Yellow solid; Yield 65 %; M.Pt. 178-180 °C; $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 4.84 (s, 2H, -OCH$_2$), 7.06 (s, 1H, Ar-H), 7.18 (dd, 1H, Ar-H), 7.28 (d, *J*= 8.0 Hz, 2H, Ar-H), 7.65 (dd, 1H, Ar-H), 7.77 (d, *J*= 8.0 Hz, 2H, Ar-H), 8.12 (m, 1H, Ar-H), 12.82 (br. s, 1H, -NHCS-); $^{13}$C NMR (DMSO-d$_6$, 75 MHz): $\delta$ 78.1, 120.6, 122.4, 123.5, 124.7, 125.6, 126.7, 127.6, 128.9, 129.8, 130.3, 133.5, 136.6, 142.3, 148.5, 162.2, 165.3; MS (ESI): m/z [(M+H)$^+$]: 455; Anal. calc. for $C_{19}H_{11}ClF_4N_4OS$: C 50.17, H 2.44, N 12.32 %. Found: C 50.18, H 2.46, N 12.35 %.

***General procedure for the preparation of 5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-N-phenyl-1,3,4-thiadiazol-2-amine derivatives (6a-d)***

A mixture of 0.001 mol of 2-(2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl) oxy) acetyl)-N-phenyl hydrazine carbothioamide (**4a**) and concentrated $H_2SO_4$ (1 mL) was stirred at room temperature for 1-2 h. Then the reaction mixture was poured over crushed ice. The precipitated solid was washed with sodium carbonate solution followed by water to afford compound .

***5-(((6-Fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-N-phenyl-1,3,4-thiadiazol-2-amine (6a).*** Light yellow solid; Yield 80 %; M.Pt. 155-157 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 4.91 (s, 2H, -$OCH_2$), 7.09 (s, 1H, Ar-H), 7.11 (dd, 1H, Ar-H), 7.26-7.31 (m, 3H, Ar-H), 7.39-7.43 (m, 2H, Ar-H), 7.63 (dd, 1H, Ar-H), 8.16 (m, 1H, Ar-H), 10.16 (br. s, 1H, -NH-); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 68.8, 121.3, 122.5, 123.3, 124.8, 125.4, 126.5, 128.9, 129.7, 130.4, 133.8, 135.3, 136.5, 142.3, 148.3, 150.2, 162.2; MS (ESI): m/z [$(M+H)^+$]: 421; Anal. calc. for $C_{19}H_{12}F_4N_4OS$: C 54.28, H 2.88, N 13.33 %. Found: C 54.29, H 2.89, N 13.35 %.

***5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-N-(3-methoxyphenyl)-1,3,4-thiadiazol-2-amine (6b).*** Yellow solid; Yield 74 %; M.Pt. 163-165 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 3.82 (s, 3H, -$OCH_3$), 4.89 (s, 2H, -$OCH_2$), 7.09 (s, 1H, Ar-H), 7.18 (dd, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.40-7.46 (m, 3H, Ar-H), 7.66 (dd, 1H, Ar-H), 8.12 (m, 1H, Ar-H), 12.85 (br. s, 1H, -NHCS-); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 55.5, 69.2, 120.5, 121.6, 122.4, 123.6, 124.3, 125.7, 126.6, 127.5, 128.7, 129.7, 131.2, 133.4, 135.6, 136.9, 142.5, 148.3, 162.3, 165.7; MS (ESI): m/z [$(M+H)^+$]: 451; Anal. calc. for $C_{20}H_{14}F_4N_4O_2S$: C 53.33, H 3.13, N 12.44 %. Found: C 53.35, H 3.15, N 12.45 %.

***5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-N-(p-tolyl)-1,3,4-thiadiazol-2-amine (6c).*** Yellow solid; Yield 60 %; M.Pt. 181-183 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 2.35 (s, 3H, -$CH_3$), 4.92 (s, 2H, -$OCH_2$), 7.07 (s, 1H, Ar-H), 7.16 (dd, 1H, Ar-H), 7.28 (d, *J*= 8.0 Hz, 2H, Ar-H), 7.63 (dd, 1H, Ar-H), 7.77 (d, *J*= 8.0 Hz, 2H, Ar-H), 8.12 (m, 1H, Ar-H), 12.86 (br. s, 1H, -NHCS-); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 21.7, 69.1, 120.3, 122.5, 123.7, 124.8, 125.5, 126.8, 127.4, 128.5, 129.7, 130.4, 133.5, 136.8, 142.4, 148.7, 162.6, 165.8; MS (ESI): m/z [$(M+H)^+$]: 435; Anal. calc. for $C_{20}H_{14}F_4N_4OS$: C 55.30, H 3.25, N 12.90 %. Found: C 55.31, H 3.28, N 12.89 %.

***N-(4-chlorophenyl)-5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-1,3,4-thiadiazol-2-amine (6d).*** Yellow solid; Yield 62 %; M.Pt. 162-164 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 4.90 (s, 2H, -$OCH_2$), 7.05 (s, 1H, Ar-H), 7.15 (dd, 1H, Ar-H), 7.26 (d, *J*= 8.0 Hz, 2H, Ar-H), 7.66 (dd, 1H, Ar-H), 7.77 (d, *J*= 8.0 Hz, 2H, Ar-H), 8.12 (m, 1H, Ar-H), 12.81 (br. s, 1H, -NHCS-); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 68.9, 120.5, 122.6, 123.5, 124.7, 125.5, 126.8, 127.6, 128.9, 129.6, 130.5, 132.4, 136.7, 142.6, 148.4, 162.3, 165.4; MS (ESI): m/z [$(M+H)^+$]: 455; Anal. calc. for $C_{19}H_{11}ClF_4N_4OS$: C 50.17, H 2.44, N 12.32 %. Found: C 50.19, H 2.45, N 12.34 %.

***General procedure for the preparation of 5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-N3-phenyl-4H-1,2,4-triazole-3,4-diamine (7a-d)***

Charged compound 2-(2-((6-fluoro-2-(trifluoromethyl)quinolin-4-yl) oxy) acetyl)-N-phenyl hydrazine carbothioamide (**4a**) (0.01 mol) with $N_2H_4.H_2O$ (0.01 mol) in MeOH (1 mL). The solution was refluxed for 5–6 h. After cooling to room temperature, ice water (10 mL) was added to the reaction mixture, which was then neutralized with 3N HCl to form a precipitate. The precipitate

was isolated by filtration to afford the triazole derivatives **7a-d**.

***5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-N3-phenyl-4H-1,2,4-triazole-3,4-diamine (7a).*** Light cream solid; Yield 82 %; M.Pt. 179-181 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 4.90 (s, 2H, -$OCH_2$), 5.19 (br. s, 2H, -$NH_2$), 6.99 (br. s, 1H, -NH-), 7.12 (s, 1H, Ar-H), 7.25 (dd, 1H, Ar-H), 7.30-7.36 (m, 3H, Ar-H), 7.45-7.48 (m, 2H, Ar-H), 7.66 (dd, 1H, Ar-H), 8.11 (m, 1H, Ar-H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 71.2, 120.3, 121.5, 123.4, 124.7, 125.5, 126.6, 128.6, 129.8, 130.5, 133.7, 136.5, 142.3, 148.3, 151.2, 156.4, 162.1; MS (ESI): m/z [$(M+H)^+$]: 419; Anal. calc. for $C_{19}H_{14}F_4N_6O$: C 54.55, H 3.37, N 20.09 %. Found: C 54.57, H 3.39, N 20.11 %.

***5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-N3-(3-methoxyphenyl)-4H-1,2,4-triazole-3,4-diamine (7b).*** Light Yellow solid; Yield 69 %; M.Pt. 181-183 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 3.83 (s, 3H, -$OCH_3$), 4.91 (s, 2H, -$OCH_2$), 5.20 (br. s, 2H, -$NH_2$), 7.01 (br. s, 1H, -NH-), 7.15 (s, 1H, Ar-H), 7.26 (dd, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 7.42-7.48 (m, 3H, Ar-H), 7.69 (dd, 1H, Ar-H), 8.13 (m, 1H, Ar-H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 55.6, 71.3, 119.8, 120.6, 122.1, 123.7, 124.6, 125.6, 126.7, 127.8, 128.9, 129.7, 131.2, 133.4, 135.6, 142.5, 148.3, 152.1, 155.6, 162.3,; MS (ESI): m/z [$(M+H)^+$]: 449; Anal. calc. for $C_{20}H_{16}F_4N_6O_2$: C 53.57, H 3.60, N 18.74 %. Found: C 53.59, H 3.62, N 18.76 %.

***5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-N3-(p-tolyl)-4H-1,2,4-triazole-3,4-diamine (7c).*** Yellow solid; Yield 62 %; M.Pt. 171-173 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 2.36 (s, 3H, -$CH_3$), 4.92 (s, 2H, -$OCH_2$), 5.21 (br. s, 2H, -$NH_2$), 7.03 (br. s, 1H, -NH-), 7.15 (s, 1H, Ar-H), 7.28 (dd, 1H, Ar-H), 7.36 (d, *J*= 8.0 Hz, 2H, Ar-H), 7.65 (dd, 1H, Ar-H), 7.78 (d, *J*= 8.0 Hz, 2H, Ar-H), 8.14 (m, 1H, Ar-H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 21.5, 71.5, 120.4, 122.6, 123.8, 124.6, 125.4, 126.7, 127.5, 128.6, 129.8, 130.5, 133.6, 136.7, 140.5, 142.5, 148.8, 152.4, 155.6, 162.6; MS (ESI): m/z [$(M+H)^+$]: 433; Anal. calc. for $C_{20}H_{16}F_4N_6O$: C 55.56, H 3.73, N 19.44 %. Found: C 55.58, H 3.75, N 19.46 %.

***N3-(4-chlorophenyl)-5-(((6-fluoro-2-(trifluoromethyl)quinolin-4-yl)oxy)methyl)-4H-1,2,4-triazole-3,4-diamine (7d).*** Yellow solid; Yield 673%; M.Pt. 192-194 °C; $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta$ 4.93 (s, 2H, -$OCH_2$), 5.21 (br. s, 2H, -$NH_2$), 7.03 (br. s, 1H, -NH-), 7.16 (s, 1H, Ar-H), 7.25 (dd, 1H, Ar-H), 7.35 (d, *J*= 8.0 Hz, 2H, Ar-H), 7.64 (dd, 1H, Ar-H), 7.79 (d, *J*= 8.0 Hz, 2H, Ar-H), 8.10 (m, 1H, Ar-H); $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 71.5, 120.4, 122.5, 123.7, 124.6, 125.6, 126.7, 127.8, 128.5, 129.3, 130.6, 132.5, 136.7, 142.6, 148.4, 151.4, 155.8, 162.3; MS (ESI): m/z [$(M+H)^+$]: 453; Anal. calc. for $C_{19}H_{13}ClF_4N_6O$: C 50.40, H 2.89, N 18.56 %. Found: C 50.42, H 2.91, N 18.58 %.

## CONCLUSION

In our research program we designed and synthesized novel triazolothione, thiadiazole, triazole functionalized quinoline derivatives. The structures of all new compounds were confirmed by comprehensive spectroscopic analysis (IR, $^1$H, $^{13}$C NMR, and ESI-MS). All the products were screened against anticancer activity on four human cancer cell lines "HeLa (cervical cancer, CCL-2), COLO 205 (colon cancer, CCL-222), HepG2 (liver cancer, HB-8065), and MCF7 (breast cancer, HTB-22)", using the MTT assay promising compounds identified. All the products were screened anti-inflammatory activity, among the compounds tested, Some of the compounds exhibited significant inhibition of IL-1b secretion as a measure of anti-inflammatory activity.

## REFERENCES


1. Zeleke D, Eswaramoorthy R, Belay Z, Melaku Y: Synthesis and antibacterial, antioxidant, and molecular docking analysis of some novel quinoline derivatives. 2020 2020.
2. Mrozek-Wilczkiewicz A, Malarz K, Cie W, Spaczy E: Eur J Med Chem 2019; 177: 338-49.
3. Wang M, et al.: Eur J Med Chem 2021; 214: 113208.
4. Murugan K, et al.: Sci Rep 2022; 12: 1-11.
5. Nayak N, Ramprasad J, Dalimba U: J Fluor Chem 2016; 183: 59-68.
6. Zhang S, et al.: Drug Discov Today 2018; 23: 18.
7. Ilakiyalakshmi M, Arumugam Napoleon A: Arab J Chem 2022; 15: 104168.
8. Jain S, Chandra V, Jain PK, Pathak K, Pathak D, Vaidya A: Arab J Chem 2019; 12: 4920-46.
9. Matada BS, Pattanashettar R, Yernale NG: Bioorg Med Chem 2021; 32: 115973.
10. Prajapati SM, Patel KD, Vekariya RH, Panchal SN, Patel HD: RSC Adv 2014; 4: 24463-76.
11. Delgado JN, Remers WA: Wilson and Gisvold's Text Book of Organic Medicinal and Pharmaceutical Chemistry. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 1998: 235-52.
12. Fournet A, Barrios AA, Muñoz V, Hocquemiller R, Cavé A, Richomme P, Bruneton J: Antimicrob Agents Chemother 1993; 37: 859-63.
13. Wright CW, Addae-Kyereme J, Breen AG, Brown JE, Cox MF, Croft SL, Gökçek Y, Kendrick H, Phillips RM, Pollet PL: J Med Chem 2001; 44: 3187-94.
14. Nicolaou KC, Gross JL, Kerr MA: J Heterocycl Chem 1996; 33: 735-46.
15. Bringmann G, Reichert Y, Kane V: Tetrahedron 2004; 60: 3539-74.
16. Chiari E, Oliveira AB, Prado MAF, Alves RJ, Galvão LMC, Araujo FG: Antimicrob Agents Chemother 1996; 40: 613-15.
17. Khan I, Zaib S, Batool S, Abbas N, Ashraf Z, Iqbal J, Saeed A: Bioorg Med Chem 2016; 24: 2361-81.
18. Pandiri S, Konda SK, Chennuri BK, Akarapu P, Kuncham M, Korra R, Bhoomandla S: Russ J Gen Chem 2024; 94: 1455.
19. Santhosh Kumar G, Poornachandra Y, Shravan Kumar G, Ratnakar Reddy K, JaheerMohmed KS, Ganesh Kumar C, Narsaiah B: Bioorg Med Chem Lett 2018; 28: 2328-37.
20. Sailu B, Hanumandlu R, Chiranjeevi A: Asian J Chem 2020; 32: 1931-40.
21. Kumar GS, Poornachandra Y, Reddy KR, Kumar CG, Narsaiah B: Synth Commun 2017; 47: 1864-73.
22. Sambasiva Rao P, Kurumurthy C, Veeraswamy B, Santhosh Kumar G, Poornachandra Y, Ganesh Kumar C, Sathish Babu V, Srigiridhar K, Narsaiah B: Eur J Med Chem 2014; 80: 184-91.
23. Chiranjeevi A, Sailu B, Hanumandlu R: Lett Org Chem 2022; 19: 111-17.
24. Sailu B, Naveen P, Udayasri B: Lett Org Chem 2024; 21: 575-82.
25. Chae J, Konno T, Ishihara T, Yamanaka H: Chem Lett 2004; 33: 314-15.
26. Sirisha B, Narsaiah B, Yakaiah T, Gayatri G, Narahari Sastry G, Raghu Prasad M, Raghu Ram Rao A: Eur J Med Chem 2010; 45: 1739-45.
27. Raghu D, Namratha V: Res J Chem Environ 2023; 27: 83-90.
28. Raghu D, Srinivas G, Rajashekar K, Namratha V: J Heterocycl Chem 2024; 61: 1-9.

29. Raghu D, Srinivas G, Rajashekar K, Namratha V: Russ J Org Chem 2024; 60: 2454.
30. Mosmann T: J Immunol Methods 1983; 56: 55-63.
31. a) Samad TA, Moore KA, Allchorme AS, Poole S, Bonventrek JV, Woolf CJ: Nature 2001; 410: 471-75; b) Satish K, Jayaram Reddy K, Sreenivas A, Sujitha P, Satishbabu V, Srigiridhar K, Rambabu Y: Eur J Med Chem 2013; 66: 305-13.
32. Gujja V, Sadineni K, Epuru MR, Rao Allaka T, Banothu V, Gunda SK, Koppula SK: Chem Biodivers 2023; 20: e202301232.
33. Yu B, Blaber M, Gronenborn AM, Clore GM, Caspar DL: Proc Natl Acad Sci USA 1999; 96: 103-08.
34. Bjellqvist B, Hughes GJ, Pasquali C, Paquet N, Ravier F, Sanchez JC, Frutiger S, Hochstrasser DF: Electrophoresis 1993; 14: 1023-31.
35. Gunda SK, Kongaleti SF, Shaik M: Int J Comput Biol Drug Des 2015; 8: 19-39.
36. Azam F, Madi AM, Ali HI: J Young Pharm 2012; 4: 184-92.
37. Futagi Y, Kobayashi M, Narumi K, Furugen A, Iseki K: Cell Mol Life Sci 2019; 76: 4905-21.
38. Laskowski RA, Swindells MB: J Chem Inf Model 2011; 51: 2778-86.
39. Dassault Systèmes Biovia: Discovery Studio Modeling Environment. San Diego: Dassault Systèmes; 2016.

HOW TO CITE: Chakravarthy Bhupathi, Raghu Dasari, Kavitha Tula, Shravan Kumar Gunda, Namratha Vaddiraju, Construction of Novel Triazolothione, Thiadiazole, Triazole Functionalized Quinoline Derivatives; Their Biological Evolutions and Docking Interactions, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 7, 4132-4147, https://doi.org/10.5281/zenodo.21470978