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# DESIGN, SYNTHESIS AND EVALUATION OF NEW QUINOLINE DERIVATIVESAS ANTI-CANCER AGENTS

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**Abstract:**
A Series of New(E)-2-(6-substituted-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4- substituted-phenyl) hydrazinecarbothioamide derivatives were designed, synthesized, characterized by respective spectral data and evaluated for anti cancer activity. Most of the synthesized compounds showed good in vitro inhibitory activities against MDA-MB-231, HeLa, SMMC-7721**.** Among the compounds **8e, 8j and 8o** having were 6,7-dichloro-2,3-dihydroquinolines fused with N-(4-substitutedphenyl)-hydrazinecarbothioamide showed poent cytotoxic activity at low concentration with $IC_{50}$ value 1.32±0.12µM, 1.15±0.13µM, 1.24±0.23µM and 1.89±0.18µM, 2.04±0.02µM, 2.27±0.12µM and 1.92±0.25µM, 2.35±0.03µM , 2.20±0.23µM, Compounds 8a, 8b were showed lower cytotoxic property in normal cell lines. The compound **8d, 8i, 8n** having 6-nitro-2,3-dihydroquinoline moiety fused with N-(4-substituted-phenyl)-hydrazinecarbothioamide showed less potent anti-cancer activity. Docking studies of all the molecules disclosed close hydrogen bond interactions with the binding site.

**Keywords:** Cancer, antioxidants, anti-inflammatory, hepatic cells, anti-proliferative activity, cicplatin

## 1.0. INTRODUCTION:

Cancer continues to remain one of the leading causes of illness and mortality worldwide. Notably, breast cancer is the leading cause of cancer-related fatalities for women. Chemotherapy, in addition to surgical and irradiation procedures, is an important alternative approach for cancer

therapy. However, the toxicity and side effects of chemotherapeutics reduce their efficacy, creating a great urge for the development of new anticancer medicines with proven mechanisms (1-2). The incorporation of nitrogen-containing heterocycles is typically an advantageous strategy in the structural alteration of natural products because nitrogen atoms can carry a positive charge and act as a hydrogen bond acceptor or donor, which has an important impact on the interaction between the molecule and its target. Quinoline has been extensively investigated as a key heterocyclic motif in the development of anticancer drugs. Quinoline derivatives' anticancer actions include inhibition of tyrosine kinases, proteasome, topoisomerase, tubulin polymerization, and DNA repair2 (3-4). Thiosemicarbazone analogues are one of the most promising groups of drugs in this therapeutic context, with a wide range of pharmacological actions and potential anticancer uses (5-8). Thiosemicarbazone analogues represent one of the most promising classes of compounds that have a variety of molecular actions with potential anticancer applications (9-11) Initially, anticancer effects of thiosemicarbazones was portrayed due to their inhibition property of ribonucleotide reductase which catalyzes the rate-restricting step of DNA synthesis. 2-formyl pyridine thiosemicarbazone is a nitrogen-containing heterocyclic thiosemicarbazone which was the first demonstrated thiosemicarbazone based anticancer compound and consequently developed as a cancer drug was, 3-aminopyridine-2-carbaldehyde thiosemicarbazone (3-AP or Triapine), and had entered the stage I and stage II clinical trial studies on patients. Molecular hybridization strategy is extensively used in drug design and discovery based on the combination of different bio-active moieties to produce new hybrids with the improved activities (12-15). These interesting findings about Thiosemicarbazone and quinolines as anticancer agents led to molecular hybridization strategy of Thiosemicarbazone and quinoline scaffolds to generate novel anticancer agents. Hence, more attractive tactics are to be evolved for designing a novel quinoline incorporated thiosemicarbazone analogues which may stand a chance for exhibiting the potential activity towards tumors. In this work, development of anticancer agents, we designed and synthesized novel quinoline-Thiosemicarbazone derivatives as anticancer activity.

## 2.0 MATERIALS AND METHODS:

### 2.1. Chemistry:

All chemicals and solvents, standard drugs have been collected from Sigma-Aldrich, HiMedia, Bangalore, India and others and were used without further purification with the exception of liquid aldehydes which were purified by using standard procedures prior to use. Melting point for all the compounds were recorded in open capillary tubes using VEEGO VMP-D Digital melting point apparatus.FTIR spectra were done on JASCO FTIR 4100 series by using KBr pellets and are reported in $cm^{-1}$.Signals of $^{1}H$ NMR and $^{13}C$ NMR spectra were measured on a BRUKER-II 400 (400 MHz NMR, $^{13}C$ NMR 100 MHz) spectrophotometer by taking TMS as internal standard. Pre-coated TLC plates were used to check the purity of the compounds and spots were visualized by using iodine vapors and ultra-violet rays.

### 2.2. Experimental procedure:

#### 2.2.1. General procedure for the synthesis of 3-((4-Substituted-phenyl)amino)-propanoic acid (3a-f) :

The compound 3-((4-Substituted-phenyl)amino)-propanoic acid (**3a-f**) were synthesized from 4-Substituted aniline (0.01 mmol) refluxed with 3-bromopropionic acid (0.05 mmol) in presence of 10% KOH. The completion of reaction is monitored by TLC. The reaction mixture is poured on crushed ice with constant stirring to get precipitate filtered and evaporated. The resulting oil

was purified by column chromatography using a mixture of petroleum ether and ethyl acetate 3:1 as the eluent to successfully afford the target products (**3a-f**) in good yield.

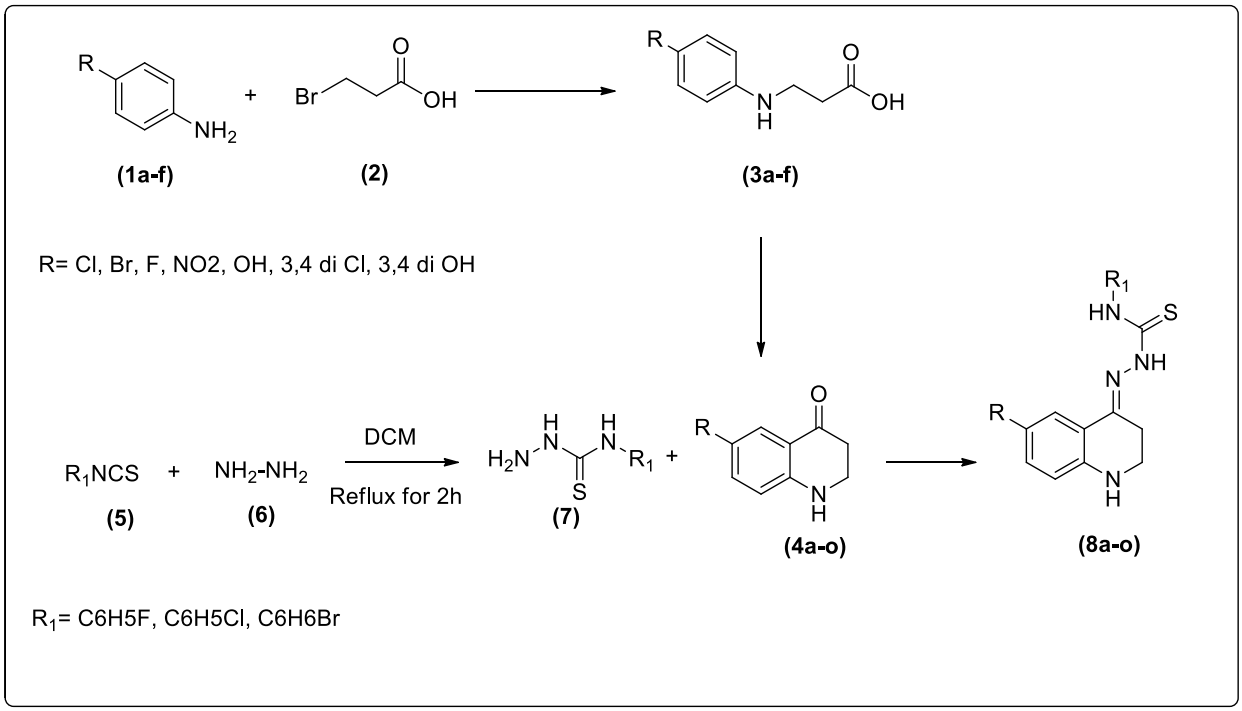
**2.2.2. General procedure for the synthesis of 6-substituted-2,3-dihydroquinolin-4(1H)-one (4a-f):** A mixtures of 3-((4-Substituted-phenyl) amino)-propanoicacid (**3a-f,** 0.034 mmol) and polyphosphoric acid (PPA) (0.025 mmol) reflux for 18 hrs. The completion of reaction is monitored by TLC. The reaction mixture is purifird by column chromatography obtained the compound cyclization and afforded a bicyclic compound purified by column chromatography using a mixture of Hexane and ethyl acetate 9:1 as the eluent to successfully afford the target products (**4a-f**) in good yield.

**2.2.3. General procedure for the synthesis of thiosemicarbazides (7) :**

To a solution of substituted isothiocyanates (**5**, 10 mmol) in dichloromethane (25 mL) was injected hydrazine hydrate (**6**, 30 mmol) portion-wise. After the mixture was stirred at room temperature for 2 h, the formed precipitation was filtered, and the left residue was washed with dichloromethane to give compounds. The reaction mixture is purifird by column chromatography obtained the compound thiosemicarbazides **(7)** in good yields.

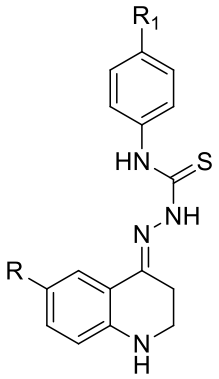
**2.2.4. General procedure for the synthesis of 6-Substituted-2,3-dihydroquinolin-4(1-H)-one derivatives (8a-o) :**

The 6-Substituted-2,3-dihydroquinolin-4(1H)-ones (**4a-f,** 0.03mmol) was dissolved in anhydrous methanol (10 mL). The solution was heated at reflux for 15 min, and then a catalytic amount of acetic acid added and a thiosemicarbazide derivatives (**7**, 1.5mmol) added. The reaction mixture was refluxed for 3-5 h after completion of the reaction (monitored by TLC), the reaction mixture was evaporated to dryness then the product was isolated by recrystallization in methanol. The pure novel quinoline incorporated thiosemicarbazone analogues obtained as dark red crystals (8a-o).



Scheme-1: synthesis of New (E)-2-(6-substituted-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4-substituted-phenyl)hydrazinecarbothioamide **(8a-o)**

**Table-1:** Physical data of synthesized compounds (E)-2-(6-substituted-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4- substituted-phenyl)hydrazinecarbothioamide **(8a-o)**.




**General structure-I** R= Cl, Br, F, $NO_2$, 3,4 Di Chloro

$R_1$= $C_6H_5F$, $C_6H_5Cl$, $C_6H_5Br$

| S.No | Comp | R | $R_1$ | Mol. Formula | Mol.wt | MP (°C) | % Yield |
|---|---|---|---|---|---|---|---|
| 1 | 8a | Cl | $C_6H_5F$ | $C_{16}H_{14}ClFN_4S$ | 348 | 88-90 | 52.23 |
| 2 | 8b | Br | $C_6H_5F$ | $C_{16}H_{14}BrFN_4S$ | 393 | 101-103 | 41.59 |
| 3 | 8c | F | $C_6H_5F$ | $C_{16}H_{14}F_2N_4S$ | 332 | 120-122 | 40.12 |
| 4 | 8d | $NO_2$ | $C_6H_5F$ | $C_{16}H_{14}FN_5O_2S$ | 359 | 92-94 | 62.83 |
| 5 | 8e | 3,4 di chloro | $C_6H_5F$ | $C_{16}H_{13}Cl_2FN4S$ | 383 | 106-108 | 40.13 |
| 6 | 8f | Cl | $C_6H_5Cl$ | $C_{16}H_{14}Cl_2N_4S$ | 365 | 102-104 | 73.93 |
| 7 | 8g | Br | $C_6H_5Cl$ | $C_{16}H_{14}BrClN_4S$ | 409 | 106-108 | 52.18 |
| 8 | 8h | F | $C_6H_5Cl$ | $C_{16}H_{14}ClFN_4S$ | 348 | 130-132 | 28.12 |
| 9 | 8i | $NO_2$ | $C_6H_5Cl$ | $C_{16}H_{14}ClN_5O_2S$ | 375 | 148-150 | 36.45 |
| 10 | 8j | 3,4 di chloro | $C_6H_5Cl$ | $C_{16}H_{13}Cl_3N_4S$ | 399 | 128-130 | 30.15 |
| 11 | 8k | Cl | $C_6H_5Br$ | $C_{16}H_{14}BrClN_4S$ | 409 | 118-120 | 65.10 |
| 12 | 8l | Br | $C_6H_5Br$ | $C_{16}H_{14}Br_2N_4S$ | 454 | 122-124 | 80.20 |
| 13 | 8m | F | $C_6H_5Br$ | $C_{16}H_{14}BrFN_4S$ | 393 | 126-128 | 63.12 |
| 14 | 8n | $NO_2$ | $C_6H_5Br$ | $C_{16}H_{14}BrN_5O_2S$ | 420 | 129-131 | 69.14 |
| 15 | 8o | 3,4 di chloro | $C_6H_5Br$ | $C_{16}H_{13}BrCl_2N_4S$ | 444 | 108-110 | 78.15 |

**3.0. Spectral data:**

**3.1. E)-2-(6-chloro-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4-fluorophenyl)hydrazine carbothioamide (8a): IR spectrum (KBr, $cm^{-1}$):** 3340.99 (NH (str)), 3058.56 (C-H Aromatic (str)), 2976.58(C-H Aliphatic (str)), 1591.58 (C=C Aromatic (str)), 1222.35(C=S(str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 7.975-8.000 (d, 1H, aromatic CH), 7.775-7.795 (d, 1H, aromatic CH), 7.672-7.679 (s, 1H, aromatic CH), 7.634-7.656 (s, 1H, aromatic CH), 7.419-7.471 (d, 1H,

aromatic CH), 7.381-7.398 (d, 1H, aromatic CH), 6.808-7.285 (d, 1H, aromatic CH), 6.267 (s, 1H, NH), 4.297 (s, 1H, aliphatic), 4.209 (s, 2H, aliphatic), 2.433 (s, 1H, aliphatic CH). 1.149 (s, 1H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**157.81,152.64, 142.08, 132.54, 131.08, 129.35, 129.09, 128.56, 128.14, 125.58, 125.27, 124.48, 114.02, 101.28, 57.20, 42.08. **MASS spectrum m/z:** 348 $[M+H]^+$, 350 $[M+2]^+$, 352 $[M+4]^+$,Calc. for $C_{16}H_{14}ClFN_4S$; CHN: C, 55.09; H, 4.05; N, 16.06; S, 9.19 Found C, 55.19; H, 4.25; N, 16.16; S, 9.20.

**3.2. (E)-2-(6-bromo-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4-fluorophenyl)hydrazine carbothioamide (8b): IR spectrum (KBr, $cm^{-1}$):** 3408.28 (NH (str)), 3045.12 (C-H Aromatic (str)), 2980.10 (C-H Aliphatic (str)), 1590.18 (C=C Aromatic(str)), 1228.45(C=S (str)).**$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.012-8.120(s, 1H, aromatic CH), 7.967-8.010 (d, 1H, aromatic CH), 7.910-7.924 (m, 2H, aromatic CH), 7.817-7.823 (m, 2H, aromatic CH), 7.684-7.694 (d, 2H, aromatic CH), 5.054 (s, 1H, NH), 2.435 (s, 2H, aliphatic CH). 1.581 (s, 2H, aliphatic CH). 1.256 (s, 1H, NH). **$^{13}$C NMR (100MHz, $CDCl_3$):**161.10, 158.18, 156.90, 149.09, 140.57, 138.14, 134.25, 130.80, 129.13, 128.48, 128.95, 120.80, 115.75, 58.12, 37.25. **MASS spectrum m/z:** 395 $[M+2]^+$, 397 $[M+4]^+$;Calc. for $C_{16}H_{14}BrFN_4S$; C, 48.86; H, 3.59; N, 14.25; S, 8.15; Found C, 48.86; H, 3.50; N, 14.24; S, 8.10.

**3.3. E)-2-(6-fluoro-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4-fluorophenyl) hydrazinecarbothioamide (8c): IR spectrum (KBr, $cm^{-1}$):** 3481.20 (NH (str)), 3062.10 (C-H Aromatic (str)), 2960.10 (C-H Aliphatic (str)), 1570.04(C=C Aromatic (str)), 1254.18(C=S, (str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.134-8.139 (d, 2H, aromatic CH), 7.960-7.978 (s, 1H, aromatic CH), 7.820-7.824 (s, 2H, aromatic CH), 7.650-7.675 (m, 2H, aromatic CH), 7.640-7.648 (s, 1H, aromatic CH), 5.059 (s, 1H, NH), 4.502 (s, 2H, aliphatic CH), 1.581 (s, 1H, aliphatic CH). 1.270 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**168.96, 148.15, 146.50, 138.50, 135.08, 130.31, 128.10, 126.10, 124.88, 122.27, 121.38, 114.32, 101.28, 57.28, 42.15,28.45 **MASS spectrum m/z:** 332 $[M+H]^+$, 334 $[M+2]^+$, 336 $[M+2]^+$.Calc. for $C_{16}H_{14}F_2N_4S$; CHN: C, 57.82; H, 4.25; N, 16.86; S, 9.65; Found C, 57.80; H, 4.20; N, 16.81; S, 9.60.

**3.4. (E)-N-(4-fluorophenyl)-2-(6-nitro-2,3-dihydroquinolin-4(1H)-ylidene) hydrazine carbothioamide(8d): IR spectrum (KBr, $cm^{-1}$):** 3420.10 (NH (str)), 3052.01 (C-H Aromatic (str)), 2980.10 (C-H Aliphatic (str)), 1580.10 (C=C Aromatic(str)), 1265.40(C=S (str)).**$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.812-8.810 (m, 3H, aromatic CH), 8.768-8.772 (d, 1H, aromatic CH), 8.240-8.245 (d, 1H, aromatic CH), 7.980-8.052 (m, 2H, aromatic CH), 7.968-7.970 (m, 2H, aromatic CH), 5.040 (s, 1H, NH), 2.410 (s, 2H, aliphatic CH). 1.541 (s, 2H, aliphatic CH). 1.250 (s, 1H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**158.10, 158.10, 158.10, 150.10, 148.50, 146.10, 134.20, 132.80, 129.13, 128.40, 127.95, 126.18, 121.18, 50.12, 48.20. **MASS spectrum m/z:** 361 $[M+2]^+$. Calc. for $C_{16}H_{14}FN_5O_2S$; C, 53.47; H, 3.93; N, 19.49; S, 8.92; Found C, 53.40; H, 3.90; N, 19.40; S, 8.90.

**3.5. (E)-2-(6,7-dichloro-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4-fluorophenyl) hydrazine carbothioamide (8e): IR spectrum (KBr, $cm^{-1}$):** 3551.56 (NH (str)), 3080.32 (C-H Aromatic (str)), 2931.73 (C-H Aliphatic (str)), 1585.20 (C=C Aromatic(str)), 1266.18(C=S (str)).**$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 7.901-7.923 (d, 1H, aromatic CH), 7.550-7.810 (m, 1H, aromatic CH), 7.654-7.681 (d, 1H, aromatic CH), 7.553-7.556 (d, 1H, aromatic CH), 7.494-7.539 (d, 1H, aromatic CH), 7.313-7.363 (m, 1H, aromatic CH), 7.093-7.130 (m, 1H, aromatic CH), 6.887-

6.911 (d, 1H, aromatic CH), 5.063 (s, 1H, NH), 5.057 (s, 1H, aliphatic CH), 3.780 (s, 2H, aliphatic CH). 2.675 (s, 1H, aliphatic CH). 1.625 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):** 153.78, 152.34, 148.50, 143.63, 142.44, 139.59, 138.74, 136.03, 129.96, 129.40, 127.96, 127.65, 126.73, 125.01, 119.69, 48.15, 38.66. **MASS spectrum m/z:** 385 $[M+2]^+$, 387 $[M+4]^+$, 389 $[M+6]^+$.Calc. for $C_{16}H_{13}Cl_2FN4S$ ;C, 50.14; H, 3.42; N, 14.62; S, 8.37; Found C, 50.10; H, 3.41; N, 14.60; S, 8.30.C, 50.14; H, 3.42; N, 14.62; S, 8.37

**3.6. (E)-2-(6-chloro-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4-chlorophenyl)hydrazinecarbothioamide (8f): IR spectrum (KBr, cm$^{-1}$):** 3420.10 (NH (str)), 3061.10 (C-H Aromatic (str)), 2968.18 (C-H Aliphatic (str)), 1578.04 (C=C Aromatic (str)), 1258.10(C=S, (str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.812-8.816 (d, 1H, aromatic CH), 8.428-8.432(d, 2H, aromatic CH), 7.960-7.978 (m, 2H, aromatic CH), 7.824-7.828 (m, 2H, aromatic CH), 7.652-7.674 (d, 1H, aromatic CH), 5.052 (s, 1H, NH), 4.508 (s, 1H, OH), 1.581 (s, 2H, aliphatic CH). 1.270 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**160.96, 156.10, 154.10, 148.50, 140.08, 138.31, 128.10, 127.10, 124.88, 122.27, 121.38, 114.32, 101.28, 57.28, 42.15, 28.45 **MASS spectrum m/z:** 365 $[M+H]^+$, 367 $[M+2]^+$, 369 $[M+4]^+$Calc. for $C_{16}H_{14}Cl_2N_4S$; CHN: C, 52.60; H, 3.38; N, 15.17; S, 7.96; Found C, 52.61; H, 3.30; N, 15.34; S, 7.90.

**3.7. E)-2-(6-bromo-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (8g): IR spectrum (KBr, cm$^{-1}$):** 3431.10 (NH (str)), 3082.18 (C-H Aromatic (str)), 2950.61 (C-H Aliphatic (str), 1585.10 (C=C Aromatic (str)), 1255.75 (C=S (str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.088-8.134 (m, 2H, aromatic CH), 7.901-7.923 (d, 1H, aromatic CH), 7.750-7.810 (m, 1H, aromatic CH), 7.654-7.681(d, 1H, aromatic CH), 7.494-7.556 (d, 1H, aromatic CH), 7.284-7.363 (d, 1H, aromatic CH), 6.887-6.911 (s, 1H, aromatic CH), 5.057 (s, 1H, NH), 2.675 (s, 2H,aliphatic CH), 1.625 (m, 2H, aliphatic CH). 1.279 (s, 1H, NH). **$^{13}$C NMR (100MHz, $CDCl_3$):**161.65, 160.15, 142.08, 132.54, 131.08, 129.05, 128.56, 128.14, 126.88, 125.27, 124.48, 114.02, 42.48, 28.56. **MASS spectrum m/z:** 409 $[M+H]^+$,411 $[M+2]^+$ , 413 $[M+4]^+$;Calc. for $C_{16}H_{14}BrClN_4S$; CHN: C, 46.90; H, 3.44; N, 13.67; S, 7.83; Found C, 46.91; H, 3.43; N, 13.63; S, 7.82.

**3.8. (E)-N-(4-chlorophenyl)-2-(6-fluoro-2,3-dihydroquinolin-4(1H)-ylidene) hydrazinecarbothioamide(8h): IR spectrum (KBr, cm$^{-1}$):** 3414.01 (NH (str)), 3061.10 (C-H Aromatic (str)), 2960.18 (C-H Aliphatic (str)), 1570.03(C=C Aromatic (str)), 1226.10(C=S (str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.812-8.815 (d, 2H, aromatic CH), 8.428-8.432(d, 2H, aromatic CH), 7.960-7.978 (d, 1H, aromatic CH), 7.835-7.842 (d, 1H, aromatic CH), 7.650-7.675 (d, 2H, aromatic CH), 5.059 (s, 1H, NH), 4.502 (s, 1H, NH), 1.581 (s, 2H, aliphatic CH). 1.270 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**160.96, 159.10, 148.50, 137.50, 135.08, 130.31, 128.10, 126.10, 124.88, 122.27, 121.38, 115.32, 105.28, 57.28, 41.10 **MASS spectrum m/z:** 348$[M+H]^+$, 350$[M+2]^+$, 352$[M+4]^+$ ; Calc. for $C_{16}H_{14}ClFN_4S$; CHN: C, 55.09; H, 4.05; N, 16.06; S, 9.19; Found C, 55.03; H, 4.01; N, 16.05; S, 9.10;

**3.9. (E)-N-(4-chlorophenyl)-2-(6-nitro-2,3-dihydroquinolin-4(1H)-ylidene)hydrazine carbothioamide (8i): IR spectrum (KBr, cm$^{-1}$):** 3430.10 (NH (str)), 3062.10(C-H Aromatic (str)), 2960.10(C-H Aliphatic (str)), 1580.01(C=C Aromatic (str)), 1263.40(C=S, (str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.820-8.823 (d, 1H, aromatic CH), 8.310-8.312 (d, 2H, aromatic CH), 7.980-7.984 (m, 2H, aromatic CH), 7.825-7.830 (d, 1H, aromatic CH), 7.610-7.612 (d, 2H, aromatic CH), 5.057 (s, 1H, NH), 3.996 (s, 1H, NH), 3.845 (s, 2H, aliphatic CH,), 1.586 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**160.16, 158.10, 157.50, 148.50, 146.08, 138.31, 128.10, 126.10, 124.88, 122.27, 121.38, 114.32, 101.28, 45.20, 39.40 **MASS spectrum m/z:**

377 $[M+2]^+$. Calc. for $C_{16}H_{14}ClN_5O_2S$; CHN: C, 51.13; H, 3.75; N, 18.63; S, 8.53; Found C, 51.10; H, 3.75; N, 18.63; S, 8.50.

**3.10. (E)-N-(4-chlorophenyl)-2-(6,7-dichloro-2,3-dihydroquinolin-4(1H)-ylidene) hydrazinecarbothioamide (8j): IR spectrum (KBr, $cm^{-1}$):** 3418.10 (NH (str)), 3050.28 (C-H, Aromatic), 2960.10 (C-H, Aliphatic), 1535.01 (C=C, Aromatic), 1275.51 (C=S). **$^1$H NMR (400MHz DMSO, δ ppm):** 8.810-8.813 (d, 2H, aromatic CH), 8.430-8.436(d, 1H, aromatic CH), 7.965-7.978 (m, 2H, aromatic CH), 7.838-7.846 (d, 2H, aromatic CH), 7.650-7.675 (d, 12H, aromatic CH), 5.059 (s, 1H, NH), 4.502 (s, 1H, NH), 1.581 (s, 2H, aliphatic CH). 1.272(s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**161.16, 158.15, 156.50, 148.15, 146.08, 138.31, 130.10, 128.10, 126.88, 124.27, 121.38, 114.32, 101.28, 56.18, 46.25. **MASS spectrum m/z:** 399 $[M+H]^+$,401 $[M+2]^+$,403 $[M+4]^+$Calc. for $C_{16}H_{13}Cl_3N_4S$; CHN: C, 48.08; H, 3.28;N, 14.02; S, 8.02, Found C, 48.18; H, 3.22; N, 14.03; S, 8.04

**3.11. (E)-N-(4-bromophenyl)-2-(6-chloro-2,3-dihydroquinolin-4(1H)-ylidene) hydrazinecarbothioamide (8k): IR spectrum (KBr, $cm^{-1}$):** 3428.10 (NH (str)), 3060.01 (C-H Aromatic (str)), 2978.11 (C-H Aliphatic (str)), 1578.12 (C=C Aromatic(str)), 1235.41 (C=S, (str)).**$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.242-8.244 (d, 2H, aromatic CH), 7.991-8.052 (d, 2H, aromatic CH), 7.841-7.856 (d, 2H, aromatic CH), 7.734-7.741 (d, 1H, aromatic CH), 7.684-7.689 (d, 1H, aromatic CH), 5.041 (s, 1H, NH), 2.410 (s, 2H, aliphatic CH). 1.544 (s, 2H, aliphatic CH). 1.281 (s, 3H, aliphatic NH). **$^{13}$C NMR (100MHz, $CDCl_3$):**161.10, 159.10, 158.10, 156.10, 148.50, 140.10, 134.25, 130.80, 129.13, 128.48, 127.95, 126.18, 120.18, 50.12, 33.15. **MASS spectrum m/z:** 409 $[M+H]^+$,411 $[M+2]^+$,413 $[M+4]^+$Calc. for $C_{16}H_{14}BrClN_4S$; C, 46.90; H, 3.44; N, 13.67; S, 7.83; Found C, 46.85; H, 3.40; N, 13.61; S, 7.80.

**3.12. (E)-2-(6-bromo-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4-bromophenyl) hydrazinecarbothioamide (8l): IR spectrum (KBr, $cm^{-1}$):** 3441.15 (NH (str)), 3072.10 (C-H Aromatic (str)), 2940.18 (C-H Aliphatic (str)), 1581.01(C=C Aromatic (str)), 1281.48(C=S (str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.230-8.234 (d, 2H, aromatic CH), 7.989-7.994 (m, 1H, aromatic CH), 7.825-7.832 (d, 2H, aromatic CH),7.820-8.824 (d, 2H, aromatic CH), 7.612-7.614 (d, 1H, aromatic CH), 5.050 (s, 1H, NH), 3.918 (s, 1H, NH), 1.580 (s, 2H, aliphatic CH), 1.278 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**160.90, 159.17, 155.10, 149.10, 144.14, 142.32, 139.10, 137.15, 128.10, 123.21, 120.38, 114.32, 101.28, 57.28, 42.15. **MASS spectrum m/z:** 454 $[M+H]^+$, 456 $[M+H]^+$, 458 $[M+H]^+$; Calc. for $C_{16}H_{14}Br_2N_4S$; CHN: C, 42.31; H, 3.11; N, 12.34; S, 7.06; Found C, 42.31; H, 3.14; N, 12.31; S, 7.03.

**3.13. (E)-N-(4-bromophenyl)-2-(6-fluoro-2,3-dihydroquinolin-4(1H)-ylidene)hydrazinecarbothioamide (8m): IR spectrum (KBr, $cm^{-1}$):** 3412.10 (NH (str)), 3050.10(C-H Aromatic (str)), 2968.10 (C-H Aliphatic (str)), 1585.04 (C=C Aromatic (str)), 1261.42 (C=S(str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.234-8.236 (d, 1H, aromatic CH), 8.135-8.138 (d, 2H, aromatic CH), 7.984-7.995 (d, 2H, aromatic CH), 7.821-7.832 (d, 1H, aromatic CH), 7.610-7.612 (d, 2H, aromatic CH), 5.050 (s, 1H, NH), 3.996 (s, 3H, NH), 3.845 1.580-1.591(m, 2H, aliphatic CH), 1.280 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**161.16, 159.11, 157.51, 149.51, 146.08, 138.35, 130.12, 128.10, 124.88, 122.27, 121.38, 114.32, 101.28, 53.23, 30.12; **MASS spectrum m/z:** 393 $[M+H]^+$, 395 $[M+H]^+$. Calc. for $C_{16}H_{14}BrFN_4S$; CHN: C, 48.86; H, 3.59; N, 14.25; S, 8.15; Found C, C, 48.81; H, 3.51; N, 14.15; S, 8.12.

**3.14. (E)-N-(4-bromophenyl)-2-(6-nitro-2,3-dihydroquinolin-4(1H)-ylidene)hydrazine carbothioamide (8n): IR spectrum (KBr, $cm^{-1}$):** 3450.10 (NH (str)), 3058.15 (C-H Aromatic (str)), 2970.18 (C-H Aliphatic (str)), 1570.02 (C=C Aromatic (str)), 1277.15 (C=S, (str)). **$^1$H**

**NMR (400MHz $CDCl_3$, δ ppm):** 8.212-8.217 (d, 1H, aromatic CH), 8.132-8.135(d, 2H, aromatic CH), 7.971-7.978 (d, 2H, aromatic CH), 7.824-7.828 (m, 2H, aromatic CH), 7.652-7.674 (m, 3H, aromatic CH), 5.031 (s, 1H, NH), 4.508 (s, 1H, NH), 1.581 (s, 2H, aliphatic CH). 1.248 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**161.10, 158.11, 156.10, 149.54, 145.08, 138.31, 129.10, 126.10, 124.88, 122.27, 121.38, 114.32, 108.28, 57.28, 42.15. **MASS spectrum m/z:** 420 $[M+H]^+$,422 $[M+2]^+$. Calc. for $C_{16}H_{14}BrN_5O_2S$; CHN: C, 45.72; H, 3.36; N, 16.66; S, 7.63; Found C, 45.70; H, 3.32; N, 16.61; S, 7.60.

**3.15. (E)-N-(4-bromophenyl)-2-(6,7-dichloro-2,3-dihydroquinolin-4(1H)-ylidene) hydrazine carbothioamide (8o): IR spectrum (KBr, $cm^{-1}$):** 3461.10 (NH (str)), 3072.18 (C-H Aromatic (str)), 2968.12 (C-H Aliphatic (str)), 1518.082 (C=C Aromatic (str)), 1370.10 (C-O(str)). **$^1$H NMR (400MHz $CDCl_3$, δ ppm):** 8.212-8.214 (d, 2H, aromatic CH), 8.135-8.138(d, 2H, aromatic CH), 7.970-7.977 (m, 2H, aromatic CH), 7.821-7.826 (d, 1H, aromatic CH), 7.665-7.671 (d, 1H, aromatic CH), 5.028 (s, 1H, NH), 4.132 (s, 1H, NH), 1.580 (s, 2H, aliphatic CH). 1.325 (s, 2H, aliphatic CH). **$^{13}$C NMR (100MHz, $CDCl_3$):**161.96, 158.10, 156.50, 138.50, 135.08, 130.31, 128.10, 126.10, 124.88, 122.27, 121.38, 114.32, 101.28, 55.18, 40.15. **MASS spectrum m/z:** 444 $[M+H]^+$, 446 $[M+2]^+$, 448 $[M+4]^+$, 450 $[M+6]^+$, Calc. for $C_{16}H_{13}BrCl_2N_4S$; CHN: C, 43.26; H, 2.95; N, 12.61; S, 7.22; Found C, 43.20; H, 2.90; N, 12.60; S, 7.28.

**4.0. Molecular Docking [16]:**

Molecular docking studies of (E)-2-(6-substituted-2,3-dihydroquinolin-4(1H)-ylidene)-N-(4- substituted-phenyl)hydrazinecarbothioamide **(8a-o)**were carried out using Schrödinger software (Schrödinger, Version 2019-1,) installed on Intel Xenon W 3565 processor and Ubuntu enterprise (version 14.04) as an operating system. The ligands were drawn by using ChemDraw 18.0. With the help of XP Visualiser (Schrödinger , Version 2019-1). The results were analyzed.

Schrodinger software (Version 2019-1; Schrodinger) (Glide module). The ligands used as inputs for docking were sketched by using ChemDraw software. Ligands were prepared using OPLS3e force field in Ligprep (Dizdaroglu et al. 2020) (Version 2019-1, Schrodinger) was used to carry out, the docking studies This minimization helps to assign bond orders, Addition of the hydrogens to the ligands. The generated output file containing the best conformations of the ligands was used for docking studies. Protein was prepared by using the protein preparation wizard (Dizdaroglu et al. 2020) (Version 2019-1, Schrodinger). Charges were assigned to the protein after addition of hydrogen atoms Generated Het states using epik at pH 7.2. The protein was pre-processed refined, modified by analyzing workspace. Atoms which are non-significant were excluded from the crystal structure. Finally, the protein was optimized by using OPLS3e force filed. A receptor grid was generated around the cocrystal ligand (X-ray pose of the ligand in the protein). Ligand centroid was selected to generate grid box, and Vander Waal radius of receptor atoms was scaled to 1.00 Å having a partial atomic charge of 0.25. From the output, The best-docked structure was determined using Glide docking score. Poses of the generated output of ligands after docking was analyzed by the help of XP Visualizer (Version 2019-1, Schrodinger). The results are presented in **Tables-2** and **Figures-1** and **2**.

**Table-2: Binding Energies (Kcal/mol), No. of HBs and Binding Sites**

| S.No | Compound | Docking score of MDA-MB-231(2LU9) | Docking score of HELA (6I2I) | Docking score of SMMC-7721 (6C41) |
|---|---|---|---|---|
| **1** | 8a | -4.971 | -4.782 | -5.122 |

| | | | | |
|---|---|---|---|---|
| **2** | 8b | -5.707 | -3.723 | -4.103 |
| **3** | 8c | -2.057 | -3.415 | -5.421 |
| **4** | 8d | -5.146 | -3.714 | -6.120 |
| **5** | **8e** | **-9.861** | **-10.395** | **-7.124** |
| **6** | 8f | -6.401 | -6.711 | -5.832 |
| **7** | 8g | -5.381 | -3.484 | -4.212 |
| **8** | 8h | -4.712 | -3.489 | -4.128 |
| **9** | 8i | -3.942 | -3.526 | -4.130 |
| **10** | **8j** | **-8.386** | **-7.475** | **-6.823** |
| **11** | 8k | -5.386 | -3.241 | -4.454 |
| **12** | 8l | -6.934 | -5.224 | -5.261 |
| **13** | 8m | -5.270 | -4.252 | -4.315 |
| **14** | 8n | -4.352 | -4.721 | -4.721 |
| **15** | **8o** | **8.101** | **-7.911** | **-7.524** |
| **16** | Cocrystal Ligand | 5.787 | -9.068 | -8.145 |

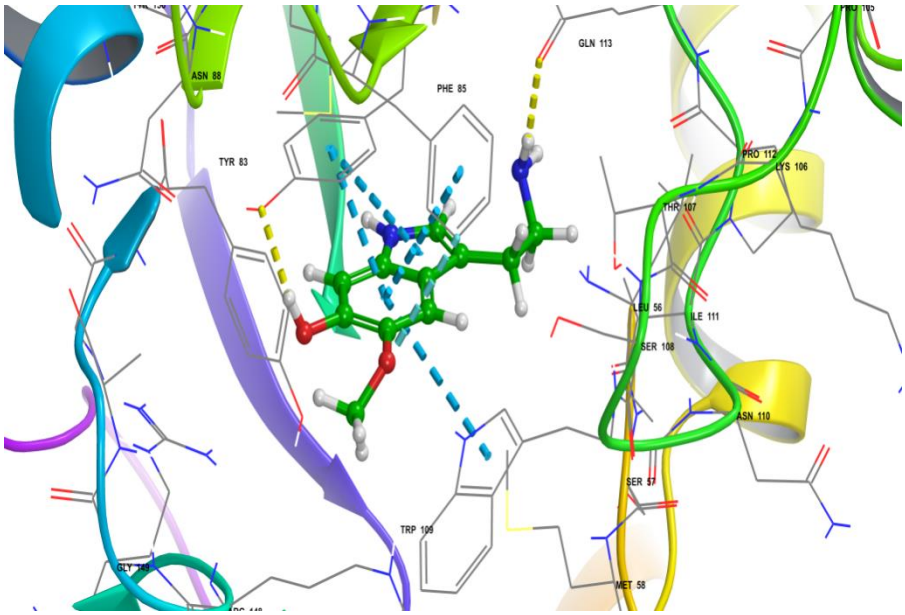



**Figure-1**: Binding poses and interactions of compound **8e** to the binding sites of target protein **MDA-MB-231(2LU9).**

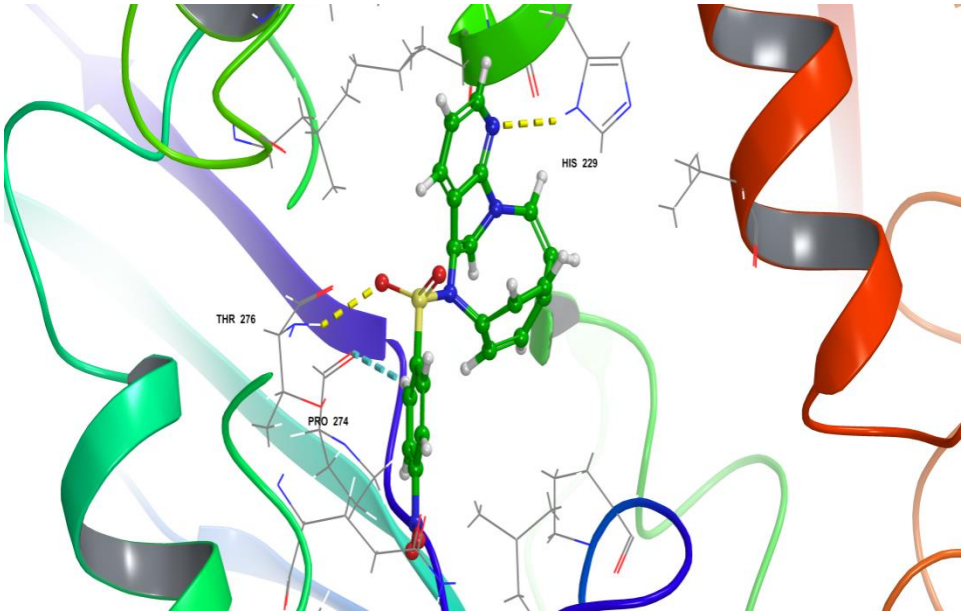



**Figure-1**: Binding poses and interactions of compound **8e** to the binding sites of target protein HELA (6I2I).

**4.1. Results and discussions:**

*In-vitro* studies of synthesized compounds showed the potential anti-cancer activity and among the compounds **8e** showed promising anti-cancer activity. These result encouraged us to perform docking studies to get the insight in to the binding mode of synthesized compounds within binding pocket of MDA-MB-231(2LU9), HeLa -6I2I) and SMMC-7721 (6C41). All structures of ligands were built using maestro and further prepared using LigPrep form Schrodinger package. Protein structures were obtained from the Protein Data Bank (PDB ID: MDA-MB-231(2LU9), HeLa -6I2I) and SMMC-7721 (6C41) necessary correction to the protein structure were done using Protein Preparation Wizard in Schrodinger package. Docking studies were performed using Glide docking software and docking protocol was validated by docking the cocrystal ligand which resulted with RMSD of docked conformation and cocrystal ligand pose was found to be 0.6. The binding interactions of compounds with MDA-MB-231(2LU9), HeLa -6I2I) and SMMC-7721 (6C41) have been listed in **Table- 1, Figure- 1 and2.**

Docking study was performed on binding poses of synthesized compounds with MCF-7 have shown that these molecules bind well within binding pocket of enzyme. Among the all synthesized molecules, compound with potent cholinesterase inhibitory activity **8e** has shown the highest binding score(-9.861 and -10.395 and -7.124against MDA-MB-231(2LU9), HeLa -6I2I) and SMMC-7721 (6C41). In superimposed pose of **8e** with cocrystal ligand, isatin ring was coinciding with skeleton of cocrystal ligand as depicted in **Figure-2.**

**4.2. Anti-cancer activity [17] :**

In vitro MTT assay for anticancer activity of novel Quinoline derivatives are known to have a wide range of biological properties, including anticancer activity. To assess the biological activity of synthesized compounds, we performed in vitro anticancer activity against breast cancer cell line (MDA-MB-231), cervical carcinoma cell line (HeLa), hepatocarcinoma cell line (SMMC-7721) using the MTT (3-(4, 5-dimethyl thiazol-2yl)-2, 5- diphenyl tetrazolium bromide) assay, as described. To begin, 1 105 cells/mL cells were planted in 96 well microtiter plates and cultured overnight in minimal essential medium with fetal bovine serum.All of the compounds

were dissolved in DMSO to attain a final concentration of 0.1M before being serially diluted with complete medium to obtain test concentrations of 0.001, 0.01, 0.1, 1.0, and 10uM. The 96-well plate was seeded with MCF-7 breast cancer cells and treated with various concentrations of the test compounds for 96 hours at 37°C with 5% CO2 concentration for maintaining the system's pH. Following that, the cells were treated with MTT reagent and incubated for further 4 hours. The supernatant from each well containing media and MTT was carefully removed, and the dark blue formazan product produced by the cells was dissolved in 100ul of DMSO. To test cell viability, absorbance at 570nm was measured using a 96-well plate reader. The percentage inhibitions were determined using the following formula and plotted against the concentrations used for calculating the $IC_{50}$ values.

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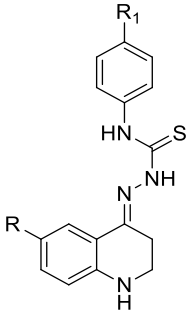
$$\% \text{ Inhibition} = \frac{\text{OD Control- OD treated} * 100}{\text{OD Control}}$$

**Table-2 :Anti-cancer activity of New substituted 4-(quinolin-4-ylamino)benzohydrazide derivatives (8a-o):**




**General structure-I (8a-o)**

| S.No | Comp | R | $R_1$ | Mol. Formula | MDA-MB-231 $IC_{50}$ (µM) | HELa $IC_{50}$ (µM) | SMMC-7721 $IC_{50}$ (µM) |
|---|---|---|---|---|---|---|---|
| 1 | 8a | Cl | $C_6H_5F$ | $C_{16}H_{14}ClFN_4S$ | 5.12±0.03 | 5.20±0.12 | 6.15±0.12 |
| 2 | 8b | Br | $C_6H_5F$ | $C_{16}H_{14}BrFN_4S$ | 4.25±0.24 | 4.84±0.18 | 4.95±0.25 |
| 3 | 8c | F | $C_6H_5F$ | $C_{16}H_{14}F_2N_4S$ | 2.28±0.13 | 2.42±0.03 | 2.26±0.03 |
| 4 | 8d | $NO_2$ | $C_6H_5F$ | $C_{16}H_{14}FN_5O_2S$ | 6.14±0.42 | 6.62±0.12 | 7.45±0.03 |
| 5 | **8e** | 3,4 di chloro | $C_6H_5F$ | $C_{16}H_{13}Cl_2FN4S$ | **1.32±0.12** | **1.15±0.13** | **1.24±0.23** |
| 6 | 8f | Cl | $C_6H_5Cl$ | $C_{16}H_{14}Cl_2N_4S$ | 6.36±0.03 | 5.96±0.03 | 7.12±0.02 |
| 7 | 8g | Br | $C_6H_5Cl$ | $C_{16}H_{14}BrClN_4S$ | 5.65±0.02 | 4.85±0.03 | 5.95±0.03 |
| 8 | 8h | F | $C_6H_5Cl$ | $C_{16}H_{14}ClFN_4S$ | 3.18±0.13 | 3.38±0.21 | 5.16±0.13 |
| 9 | 8i | $NO_2$ | $C_6H_5Cl$ | $C_{16}H_{14}ClN_5O_2S$ | 7.11±0.12 | 7.60±0.32 | 8.45±0.13 |
| 10 | **8j** | 3,4 di chloro | $C_6H_5Cl$ | $C_{16}H_{13}Cl_3N_4S$ | **1.89±0.18** | **2.04±0.02** | **2.27±0.12** |
| 11 | 8k | Cl | $C_6H_5Br$ | $C_{16}H_{14}BrClN_4S$ | 6.84±0.14 | 5.86±0.22 | 7.35±0.28 |
| 12 | 8l | Br | $C_6H_5Br$ | $C_{16}H_{14}Br_2N_4S$ | 5.86±0.13 | 5.02±0.10 | 6.08±0.24 |
| 13 | 8m | F | $C_6H_5Br$ | $C_{16}H_{14}BrFN_4S$ | 3.78±0.08 | 2.91±0.02 | 3.12±0.12 |
| 14 | 8n | $NO_2$ | $C_6H_5Br$ | $C_{16}H_{14}BrN_5O_2S$ | 7.92±0.05 | 7.31±0.12 | 8.65±0.20 |
| 15 | **8o** | 3,4 di chloro | $C_6H_5Br$ | $C_{16}H_{13}BrCl_2N_4S$ | **1.92±0.25** | **2.35±0.03** | **2.20±0.23** |
| 16 | Cisplatin | | - | - | 1.14±0.05 | 0.95±0.02 | 1.02±0.22 |

**4.2. Results and Discussions:**

Quinoline is an efficient scaffold for anticancer drug development as its derivatives have shown potent results through several mechanisms like growth regulators through ‘‘apoptosis, disruption of cell migration, inhibition of angiogenesis, modulation of nuclear receptor responsiveness and cell cycle arrest, etc.,” The potential of quinoline derivatives has been proved in several cancer cell lines like breast cancer, colon cancer, lung cancer, colorectal cancer, renal cancer, etc. The Effect of new synthesized quinoline- Thiosemicarbazide derivatives for the evaluation of anti cancer activity was examined. We evaluated our compounds for their anti-proliferative activity for breast cancer cell line (MDA-MB-231), cervical carcinoma cell line (HeLa), hepatocarcinoma cell line (SMMC-7721). The study finding that among all the compounds **8e, 8j, 8k** were 6,7-dichloro-2,3-dihydroquinolines fused with N-(4-substitutedphenyl)-hydrazinecarbothioamide showed poent cytotoxic activity at low concentration with $IC_{50}$ value 1.32±0.12μM, 1.15±0.13μM, 1.24±0.23μM and 1.89±0.18μM, 2.04±0.02μM, 2.27±0.12μM and 1.92±0.25μM, 2.35±0.03μM , 2.20±0.23μM, The Compound 6-flouro-2,3-dihydroquinoline fused with N-(4-flouro-phenyl)-hydrazinecarbothioamide**(8c)** showed maximum potent anti-cancer activity with $IC_{50}$ value of 2.28±0.13 μM , 2.42±0.03μM and 2.26±0.03μM. Our results also showed that some of the synthesized products exhibited a moderate to strong growth inhibition activity on the tested cell lines between 0.001 and 10 μM concentrations in compared with reference anticancer drug Cisplatin. The compound **8d, 8i, 8n** having 6-nitro-2,3-dihydroquinoline moiety fused with N-(4-substituted-phenyl)-hydrazinecarbothioamide showed less potent anti-cancer activity.

**4.3. Conclusions:**

A series of new quinolines bearing N-(4- substituted-phenyl)-hydrazinecarbothioamide were designed, synthesized and evaluated as potential anti-cancer activty. Compounds **8e, 8j, 8k** exhibited potent and broad spectrum antiproliferative activity with $IC_{50}$ value of lower than 10 mM against three human tumor cell lines, and compound **8e** was found to be the most potent antiproliferative agent. Moreover, the representative compound **8e** effectively inhibited cancer growth 1.32±0.12μM, 1.15±0.13μM, 1.24±0.23μM against breast cancer cell line (MDA-MB-231), cervical carcinoma cell line (HeLa), hepatocarcinoma cell line (SMMC-7721) compared with the standard Cisplatin. Taken together, this quinoline derivatives may be a promising chemotherapeutic agent for the management of human cancer.

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