Synthesis and Biological Evaluations of N-(4-Substituted Phenyl)-7-Hydroxy-4-Methyl-2-Oxoquinoline-1(2H)-Carbothioamides

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ABSTRACT
In continuance of search for new compounds we report herein the expedient and optimized synthesis of a series of N-(4-substituted phenyl)-7-hydroxy-4-methyl-2-oxoquinoline-1(2H)-carbothioamides (5a-g) in good yields. The anticancer and antioxidant activities were determined as per the standard protocol. Nearly 5 dozens of cancer cell lines derived from nine different panels are used in the study and anticancer activity was calculated as growth percents (GPs) and percent growth inhibitions (%GIs). The molecular docking simulation against one of the potential targets i.e., epidermal growth factor receptor (EGFR) was done to find the putative approach of action of the title compounds 5a-g. N-(4-Nitrophenyl)-7-hydroxy-4-methyl-2-oxoquinoline-1(2H)-carbothioamides (5b) showed the most promising anticancer activity with higher sensitivity against UO-31, HOP-92, CAKI-1, LOX IMVI and T-47D with GPs of 66.65, 72.63, 85.80, 86.11, and 86.96 respectively. The compound 5b exhibited antioxidant activity with an IC50 value of 15.21 ± 1.52 μM. The molecular docking simulation showed an efficient binding of compound 5b against the activity site of EGFR with two H-bond interactions with the residues Gln791 and Thr854, a π-π stacking and a π-cationic interaction with the residue Phe856, while a salt bridge interaction with the residue Lys745.
1. Introduction

Quinoline a bicyclic fused aromatic scaffold plays an important role in medicinal chemistry. Many quinoline derivatives are also widely used as pharmaceuticals. They are used as antimalarial,\(^1\)–\(^3\) antitubercular,\(^4\) antiviral,\(^5\) antibacterial,\(^6,7\) antihelmintic,\(^8\) local anaesthetic,\(^9\) antiasthmatic,\(^10\) cardiotonic,\(^11\) antipsychotic,\(^12\) antiglucoma,\(^13\) etc. Exatecan, topotecan, and irinotecan are some of the quinolines anticancer drugs used in clinical practice since the introduction of camptothecan.\(^14\)–\(^16\) The structure of some of the quinoline-based drugs are shown in Figure 1. The quinoline scaffold plays an important role in the development of anticancer drug and its analogues exhibited excellent results through different modes of action.\(^16\),\(^17\) The epidermal growth factor receptor (EGFR) is one among the various targets of anticancer agents.\(^18\) Intracellular signaling mediated by EGFR regulates many of the functions needed for cell growth, migration, and proliferation.\(^19\) In human cancer the EGFR is found to be over-expressed and/or mutated.\(^20\) The inhibition of EGFR could be a potential approach to treat cancer. The anti-EGFR activity quinoline congeners were well documented in the literature.\(^21\)–\(^24\)

Cancer is a dreadful disease that can affect any part of the body and 18.1 million new cases reported worldwide in 2018. Nearly 9.6 million deaths were registered in 2018, and in the next few decades the situation will become more appalling.\(^25\) We reported the cytotoxicity of quinoline analogues in our previous work,\(^26,27\) and in continuance for the search of new compounds for cancer therapeutics, we report herein the synthesis of new quinoline analogues with their biological activities as well as molecular docking simulation against EGFR.

2. Experimental

Synthesis of 7-hydroxy-4-methyl coumarin (3)

A solution of resorcinol (1) (50 mmol; 5.505 g) in ethyl acetoacetate (2) (50 mmol; 6.505 g, ~6.5 mL) was added slowly into previously cooled concentrated H\(_2\)SO\(_4\), stirred the reaction
mixture and maintained the temperature below 10 °C for half an hour.\textsuperscript{26,27} The reaction mixture was then poured onto the crushed ice, filtered, washed, dried and further re-crystallized with ethanol to obtain 7-hydroxy-4-methyl coumarin (3).

**Synthesis of N-(4-substituted phenyl)-7-hydroxy-4-methyl-2-oxoquinoline-1(2H)-carbothioamides (5a-g)**

An equimolar amount of 7-hydroxy-4-methyl coumarin (3) (1 mmol; 176 mg) and substituted phenyl thiourea (4a-g) (1 mmol) was fused together at 200 °C on oil bath for 1 h. The reaction mixture was then cooled and 5 mL ethanol was added followed by the addition of 5 mL water. The separated solid was collected by vacuum filtration, washed with water, dried and re-crystallizes from ethanol.

**Anticancer activity**

The *in vitro* anticancer activity of the compounds (5a-g) was determined on nine different panels of cancer cell lines. There were nearly 5 dozens cancer cell lines derived from nine different panels of breast, colon, CNS, leukemia lung, melanoma, ovarian, prostate and renal cancer cell lines used in the present investigation. The anticancer activity was recorded as growth percents (GPs) and percent growth inhibitions (%GIs). The anticancer activity was done as per the standard protocol followed by National Cancer Institute US.\textsuperscript{28–31}

**Antioxidant activity**

1,1-Diphenyl-2-picrylhydrazyl (DPPH) free radicals (FR) scavenging activity was undertaken to evaluate the antioxidant activity of the title compounds (5a-g) according to the reported method by Koleva et al., 2002 and IC\textsubscript{50} (50% free radical scavenging activity) was recorded in μM.\textsuperscript{32}

**Molecular docking studies**

The molecular docking against EGFR was performed for the ligands, 5a-g. The EGFR (PDB: 3W2R) X-ray crystal structure with a resolution of 2.05 Å; R-value 0.220 (observed) was obtained.
from the protein data bank. The ligands 5a-g were saved as mol file and the docking was done as per the protocol reported by Sogabe et al.

3. Results and discussions

Chemistry

The 7-hydroxy-4-methyl coumarin (3) was synthesized from an equimolar amount of resorcinol (1) and ethyl acetoacetate (2) as per the reported method. The synthetic protocol of compound 3 is summarized in Scheme 1. The second step involves fusion of an equimolar amount of 7-hydroxy-4-methyl coumarin (3) and substituted phenyl thiourea (4a-g) at 200 °C in oil bath for 1 h to obtain N-(4-substituted phenyl)-7-hydroxy-4-methyl-2-oxoquinoline-1(2H)-carbothioamides (5a-g) and the synthetic protocol is shown in Scheme 2. The substituted phenyl thiourea (4a-g) was synthesized by the previous reported method. Infrared (IR), nuclear magnetic resonance (NMR), and mass spectral data were used to validate the structure of target compounds (5a-g).

The IR spectra of the prototype compound 5b revealed stretching vibrations of phenolic (OH), carbonyl (C=O), S=C, and NH at 3402, 3223, 1682, and 1268 cm⁻¹, respectively. The ¹H NMR of compound 5b showed three singlet peaks at 2.34, 6.10 and 6.68 ppm for the three protons of CH₃, one aromatic proton (adjacent proton of 4-methyl) and one aromatic proton of the coumarin (adjacent of phenolic function), while a doublet for two protons of coumarin was observed at 6.80 ppm. The aromatic protons of nitrophenyl aromatic ring was found to have two doublets, each with two protons, at 7.38 and 7.55 ppm, while two singlet peaks at 8.58 and 10.50 ppm were observed for the ArNH and ArOH protons respectively. The ¹³C NMR of compound, 5b showed a C=S function at δ 161.15 ppm, while the carbonyl function was observed at 160.29 ppm. The methyl function was observed at 18.06 ppm, while the rest of the aromatic carbons were observed at 156.30, 154.84, 154.46, 153.48, 126.55, 120.29, 119.54, 113.79, 112.85, 112.02, 110.25, and 102.18 ppm. The mass spectra of compound 5b revealed two peaks for the M⁺ and (M + 1)⁺, respectively, at 355.0 and 356.1.

Optimization of reaction

Prior to the synthesis of the target compounds, the reaction conditions were optimized in order to obtain a high yields of products in a short amount of time. A mixture of compound 3 and 4a was subjected to various reaction conditions as shown in Table 1. The yields of the reaction were found to be 68% in methanol (entry 1) and 70% in ethanal (entry 1) with a reaction time of 10 h. The yields of the product were found to less (than alcohols) in dioxane (62%; entry 3) and dimethylsulfoxide (DMSO) (67%; entry 5) with a reaction time of 12 h. The yield was found to be least in the solvent toluene (38%; entry 6) with reaction time of 8 h. The yield was further increased to 72% (entry 4) when the reaction was carried out in glacial acetic acid (GAA) for 2 h. The yield was found to be the highest (88%; entry 7) when the reaction was carried out at high temperature (200 °C) in solvent-free conditions. Finally, all the target compounds (5a-g) were synthesized by
two different methods, one by refluxing the reaction mixture in the solvent GAA and other by fusing the reaction mixture in solvent free at elevated temperature (200 °C) on oil bath. The physical constants and yields of the target compounds (5a-g) are shown in Table 2.

**Anticancer activity**

Polycyclic aromatic compounds were reported as biologically active compounds. The scaffold quinoline was also evaluated as anticancer agent. The anticancer activity of target compounds (5a-g) was calculated as GP and %GI at 10 μM on nearly 5 dozen cancer cell lines derived from breast, colon, CNS, leukemia lung, melanoma, ovarian, prostate and renal cancer cell lines. All the compounds showed promising results and showed maximum sensitivity against UO-31 (renal cancer) cell line with GP 66.65 to 84.53. The anticancer activity of the compounds (5a-g) against the five most sensitive cell
Table 3. The anticancer activity of oxoquinoline-1(2H)-carbothioamides (5a-g).

| Compound/NSC code | Cancer cell lines assay in single dose assay 10 μM concentration | The most sensitive cell lines | GP % | GI % |
|-------------------|---------------------------------------------------------------|-----------------------------|------|------|
| 5a    | UO-31 (Renal Cancer)                                         | 72.15                       | 27.85|
|       | NSC 805507                                                   | SK-OV-3 (Ovarian Cancer)    | 79.14| 20.86|
|       |                                                               | NCI-H226 (Non-Small Cell Lung Cancer) | 80.50| 19.50|
|       |                                                               | HOP-62 (Non-Small Cell Lung Cancer) | 84.07| 15.93|
|       |                                                               | HOP-92 (Non-Small Cell Lung Cancer) | 84.58| 15.42|
| 5b    | UO-31 (Renal Cancer)                                         | 66.65                       | 33.35|
|       | NSC 805504                                                   | HOP-92 (Non-Small Cell Lung Cancer) | 72.63| 27.37|
|       |                                                               | CAKI-1 (Renal Cancer)       | 85.80| 14.20|
|       |                                                               | LOX IMVI (Melanoma)         | 86.11| 13.89|
|       |                                                               | T-47D (Breast Cancer)       | 86.96| 13.04|
| 5c    | UO-31 (Renal Cancer)                                         | 79.09                       | 20.91|
|       | NSC 803506                                                   | NCI-HS22 (Non-Small Cell Lung Cancer) | 86.80| 13.20|
|       |                                                               | SK-OV-3 (Ovarian Cancer)    | 87.65| 12.35|
|       |                                                               | SNB-75 (CNS Cancer)         | 88.69| 11.31|
|       |                                                               | CAKI-1 (Renal Cancer)       | 88.94| 11.06|
| 5d    | UO-31 (Renal Cancer)                                         | 84.53                       | 15.47|
|       | NSC 805503                                                   | MALME-3M (Melanoma)         | 87.97| 12.03|
|       |                                                               | CAKI-1 (Renal Cancer)       | 89.86| 10.14|
|       |                                                               | SF-539 (CNS Cancer)         | 90.72| 9.28 |
|       |                                                               | SK-OV-3 (Ovarian Cancer)    | 90.82| 9.18 |
| 5e    | UO-31 (Renal Cancer)                                         | 67.38                       | 32.62|
|       | NSC 805502                                                   | CAKI-1 (Renal Cancer)       | 86.69| 13.31|
|       |                                                               | HOP-62 (Non-Small Cell Lung Cancer) | 91.51| 8.49 |
|       |                                                               | MALME-3M (Melanoma)         | 91.81| 8.19 |
|       |                                                               | SK-OV-3 (Ovarian Cancer)    | 92.41| 7.59 |
| 5f    | UO-31 (Renal Cancer)                                         | 78.60                       | 21.40|
|       | NSC 805505                                                   | SK-OV-3 (Ovarian Cancer)    | 85.55| 14.45|
|       |                                                               | HOP-62 (Non-Small Cell Lung Cancer) | 86.74| 13.26|
|       |                                                               | T-47D (Breast Cancer)       | 87.48| 12.52|
|       |                                                               | SNB-75 (CNS Cancer)         | 88.06| 11.94|
| 5g    | UO-31 (Renal Cancer)                                         | 71.19                       | 29.81|
|       | NSC 805501                                                   | HOP-92 (Non-Small Cell Lung Cancer) | 84.05| 15.95|
|       |                                                               | CAKI-1 (Renal Cancer)       | 86.38| 13.62|
|       |                                                               | SK-OV-3 (Ovarian Cancer)    | 89.41| 11.59|
|       |                                                               | HOP-62 (Non-Small Cell Lung Cancer) | 91.93| 8.07 |
| Imatinib<sup>a</sup> |                                 |                              |      |      |
|       | HT29 (Colon Cancer)                                          | 52.9                        | 47.1 |
|       | NSC 759854                                                   | HOP-92 (Non-Small Cell Lung Cancer) | 56.3 | 43.7 |
|       |                                                               | MDA-MB-468 (Breast Cancer)  | 70.9 | 29.1 |
|       |                                                               | SF-539 (CNS Cancer)         | 75.5 | 24.5 |
|       |                                                               | SK-MEL-S (Melanoma)         | 77.7 | 22.3 |

<sup>a</sup>The anticancer data of Imatinib was retrieved from National Cancer Institute database with NSC code 759854.<sup>28</sup>

The order of anticancer activity followed with the substitutions on the phenyl ring as 4-NO2 > 4-Cl > 3-Cl > 2,4-(CH3)2 > 4-OC2H5 > 4-C2H5 > 2-C2H5.

**Antioxidant activity**

Free radicals generation by oxidative stress could be a potential threat to aggravate malignancy. Polycyclic compounds including quinoline analogues were well documented as antioxidants.<sup>40,46</sup>
The phenolic (Ar-OH) groups act as antioxidants in a variety of ways because they are strong hydrogen donors. The oxoquinoline analogues reported herein contain phenolic function and can act as antioxidant. Hence the antioxidant activity was also performed and calculated as an IC$_{50}$ (in $\mu$M) for the target compounds as per the standard protocol. Ascorbic acid was taken as positive control in the study. The title compounds (5a-g) showed antioxidant activity with IC$_{50}$ values ranging between 15.21 ± 1.52 and 84.12 ± 8.29 $\mu$M. The compounds 5a, 5b and 5c showed significant antioxidant with IC$_{50}$ values of 18.71 ± 1.81, 15.21 ± 1.52, and 22.02 ± 2.21 $\mu$M, respectively. Rest of the compounds showed moderate to less antioxidant activity. The order of antioxidant activity followed with the substitutions on the phenyl ring as 4-NO$_2$ > 4-Cl > 3-Cl > 4-OC$_2$H$_5$ > 4-C$_2$H$_5$ > 2,4-(CH$_3$)$_2$ > 2-C$_2$H$_5$. The antioxidant activity of the compounds is given in Table 4.

### Molecular docking studies

The molecular docking studies against EGFR was done as per the reported protocol. Various types of interactions including H-bond, $\pi-\pi$ stacking, $\pi$-cationic, salt bridge and halogen bond were observed in the molecular docking studies and the results of docking studies are summarized in Table 5. The compounds 5a, 5b, 5c and 5f showed two H-bonds and $\pi-\pi$ stacking interaction within the active site of EGFR. A H-bond between the phenolic function and the residue Gln791 and another H-bond between the amino function with the residue Thr854, while a $\pi-\pi$ stacking interaction between the substituted phenyl ring and the residue Phe856 was observed. The compounds 5d and 5g showed two H-bonds, one between the carbonyl function of oxoquinoline ring and the residue Met797 and another between the atom S (of carbothimide function) and the residue Thr854. One additional H-bond was also observed between the phenolic function and the residue Asp855 in the compound 5d. The most promising compound (5b) showed H-bond interaction of phenolic function with residue Gln791, H-bond interaction amino with the residue Thr854, $\pi-\pi$ stacking and $\pi$-cationic interaction of phenyl ring and ‘N’ atom nitro function with the residue Phe856, and a salt bridge interaction with the ‘O’ atom of nitro substituent with the residue Lys745. The molecular docking of ligands (5a-g) against the active site of EGFR is given in Table 5.

### Table 4. The antioxidant activity of compounds 5a-g.

| S. no. | Compound | Free radical scavenging activity IC$_{50}$ ($\mu$M) |
|--------|----------|----------------------------------|
| 1      | 5a       | 18.71 ± 1.81                     |
| 2      | 5b       | 15.21 ± 1.52                     |
| 3      | 5c       | 38.19 ± 3.81                     |
| 4      | 5d       | 56.32 ± 5.61                     |
| 5      | 5e       | 84.12 ± 8.29                     |
| 6      | 5f       | 22.02 ± 2.21                     |
| 7      | 5g       | 59.88 ± 5.98                     |
| 8      | Ascorbic acid | 14.02 ± 1.39               |

### Table 5. The molecular docking studies of ligands 5a-g against the active site EGFR.

| S. no. | Ligand | Docking score | Types of interaction |
|--------|--------|---------------|----------------------|
| 1      | 5a     | −9.066        | H-bond (Gln791), H-bond (Thr854), $\pi-\pi$ Stacking (Phe856) |
| 2      | 5b     | −9.220        | H-bond (Gln791), H-bond (Thr854), $\pi-\pi$ Stacking (Phe856), $\pi$-Cation (Phe856), Salt bridge (Lys745) |
| 3      | 5c     | −8.625        | H-bond (Gln791), H-bond (Thr854), $\pi-\pi$ Stacking (Phe856) |
| 4      | 5d     | −7.902        | H-bond (Met793), H-bond (Asp855), H-bond (Thr854) |
| 5      | 5e     | −6.347        | No interaction |
| 6      | 5f     | −9.630        | H-bond (Gln791), H-bond (Thr854), $\pi-\pi$ Stacking (Phe856), Halogen bond (Lys745) |
| 7      | 5g     | −8.899        | H-bond (Met793), H-bond (Thr854) |
The site of EGFR tyrosine kinase is shown in Figure 2. The images of 2D interactions of compounds 5a and 5b are shown in Figure 3, while 3D interactions are shown in Figure 4. The 2D and 3D interactions of rest of the compounds are given in the supplementary material (Figure 1S and Figure 2S).

4. Conclusion

An efficient and optimized synthesis of a series of \(N\)-(4-substituted phenyl)-7-hydroxy-4-methyl-2-oxoquinoline-1(2\(H\))-carbothioamides (5a-g) was brought about in good yields. All the
compounds were evaluated for their anticancer and antioxidant activities. Anticancer activity was tested against 5 dozens of cancer cell lines derived from nine different panels. All the compounds showed significant activity with higher selectivity against UO-31 (renal cancer cell line). Some of the title compounds (5a, 5b and 5f) also showed promising results in the antioxidant screening. The most promising compound 5b showed significant biological activities. All the compounds (except 5e) showed efficient binding within the active site of EGFR by different types of interaction including H-bonding, π-π stacking and π-cationic interactions with the various residues present in the active site. Further advancement and structural modification to increase anticancer activity are ongoing in our laboratory.

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Disclosure statement

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