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# Synthesis of *N*-Alkyl-3-[2-oxoquinolin-1(2*H*)-yl]propanoic Acid Derivatives and Related Compounds: Cytotoxicity and EGFR Inhibition of Some Propanamide Derivatives

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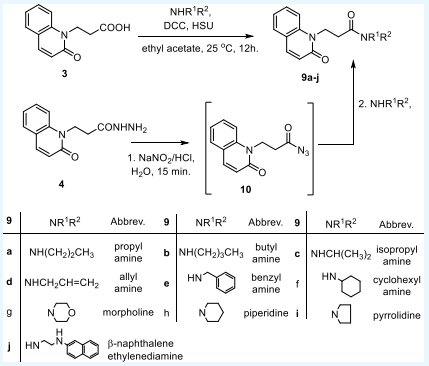
**ABSTRACT:** A series of 20 new structure-modified quinolin-2-one derivatives were prepared for biological evaluation. This was successfully achieved based on chemoselective reactions of heterocyclic amides with acrylic acid derivatives, which gave 3-[2-oxoquinolin-1-(2*H*)-yl] propanoic acid derivatives (N-substitution via a unique behavior). The ester was reacted with hydrazine to afford the corresponding hydrazide. Both the corresponding ester and hydrazide were used as building blocks to modify the quinolone structure and give *N*-hydroxyl propanamides, oxadiazoles, and thiosemicarbazides. The corresponding carboxylic acid and hydrazide were used to prepare several amides: *N*-alkyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamides via azide and dicyclohexyl carbodiimide coupling methods. Among derivatives, compound **9e** exhibited potent cytotoxicity against MCF-7 cells with an $IC_{50}$ value of 1.32 $\mu$M compared to doxorubicin with an $IC_{50}$ value of 1.21 $\mu$M. Additionally, it caused potent EGFR inhibition by 97% with an $IC_{50}$ value of 16.89 nM compared to Erlotinib with an $IC_{50}$ value of 29.8 nM. Finally, the binding mode of compound interactions toward EGFR was highlighted using a molecular docking study; compound **9e** exhibited good binding affinity with a binding energy of −17.89 kcal/mol, and it formed H-bond interactions with Met 769 as the key amino acid of interaction. Accordingly, compound **9e** may be developed as an EGFR-oriented chemotherapeutic antibreast cancer agent.




## INTRODUCTION

Cancer is a leading cause of death worldwide. The need to discover effective therapies and strategies to lessen the destructive consequences of cancer, a life-threatening disease that falls under a vast range of diseases, is even more pressing given that it kills millions of people annually and is one of the chief unsolved health challenges in contemporary medicine.[1]

A thorough comprehension of their differences and the development of tailored medicines are essential for the fight against these tumors. The lack of definitive treatment, despite tremendous scientific progress, keeps pushing the demand for novel methods and therapies.[2] This emphasizes the need to develop specific, focused treatments to combat this illness and alleviate the suffering that it causes to millions of individuals and their families globally. Cancer patients often undergo chemotherapy, which includes the use of chemotherapeutic medicines and antihormonal drugs. In contrast, adverse effects from chemotherapy might differ from one patient to another.[3,4]

Worldwide, unchecked cell growth is the driving force behind breast cancer, making it one of the most dangerous diseases in the world. The molecular composition of cancer has been better understood, but effective treatment methods are still a mystery primarily because of the limitations and adverse effects of conventional chemotherapy. The development of a safe cancer therapy option is a top priority for medicinal chemists and researchers worldwide.[5]

Conversely, quinolines are important heterocyclic moieties that have several biological uses. Since their discovery in 1842, quinolines have played a crucial role in the development of new drugs. Among the many biological uses of quinolines are their anticancer properties. Quinoline scaffold derivatives have shown promising anticancer effects through many pathways, including as apoptosis, growth suppression through cell cycle arrest, angiogenesis inhibition, cell migration disruption, and nuclear receptor responsiveness regulation.[6−11]

These findings opened new possibilities for creating anticancer drugs using quinoline motifs. Currently, clinical trials are underway for four novel anticancer agents: three protein kinase inhibitors "pelitinib, neratinib, bosutinib,

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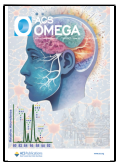


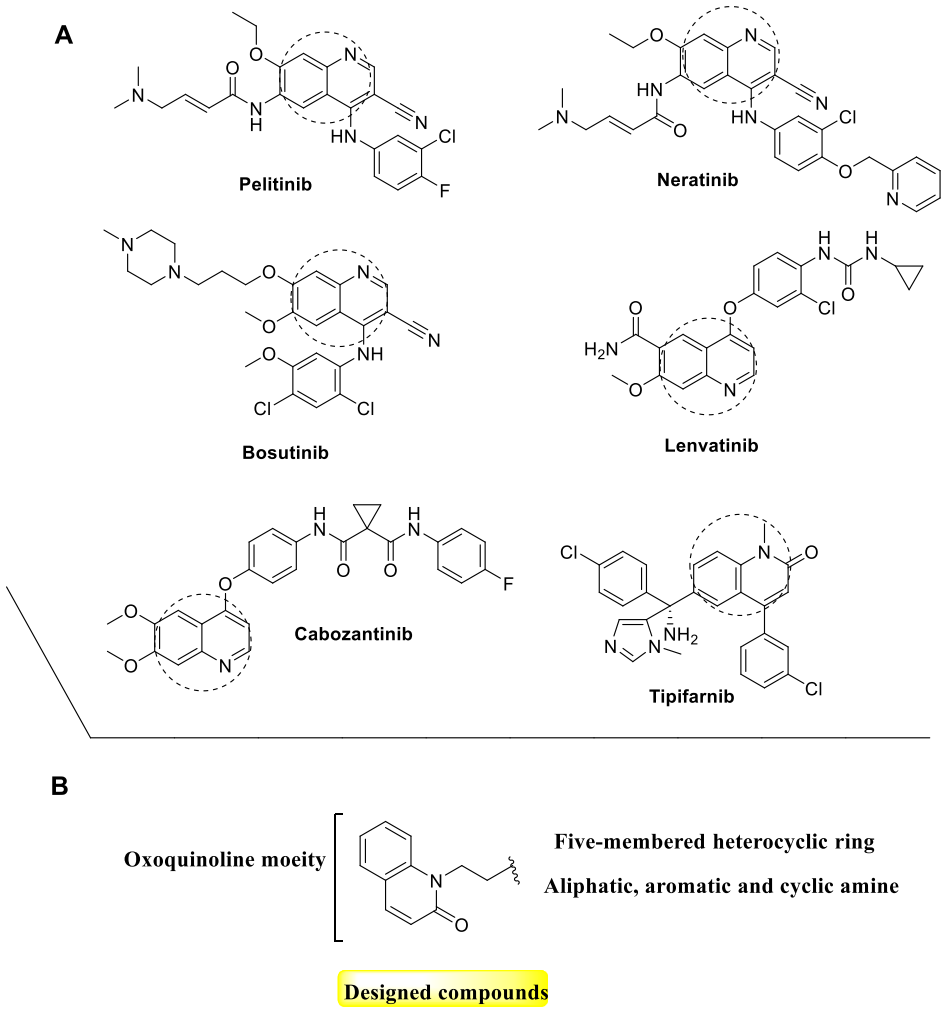
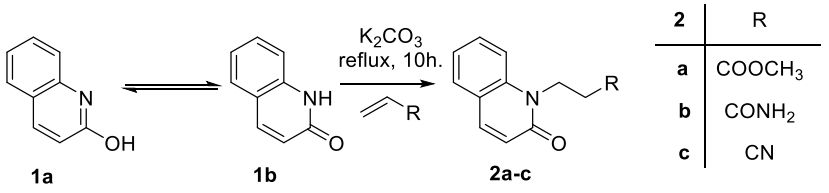



**Figure 1.** (A) Some quinoline-based anticancer drugs are kinase inhibitors. (B) Design strategy for the synthesized compounds.

**Scheme 1. Preparation of 3-[2-Oxoquinolin-1-(2*H*)-yl]propanoic Acid Derivatives 2a−c**




lenvatinib, and cabozantinib" and one farnesyltransferase inhibitor "tipifarnib" (Figure 1).[6,12−15]

2-Quinolone chemistry gained extensive investigation from the medicinal and synthetic organic chemistry view. Quinolin-2-one has a very diverse reactivity at the 1, 2, 3, 4, 5, and 6 positions. It contains an ambident nucleophilic character from competing N and O atoms, which is responsible for orienting the reaction with electrophiles. Thus, quinolin-2-one selectively gave the N-substituted quinolin-2-one by the reaction with electrophiles; alkyl halides, aroyl halides in the presence of bases; potassium carbonate, sodium hydride, KOH, and cesium carbonate at room temperature to 80 °C in DMF and, in some cases, under inert atmosphere.[16−20] Alkylation using unsaturated compounds afforded the N-substituted quinolone in 7% yield by the reaction with *N*-(quinolin-6-yl) acrylamide in the presence of palladium diacetate in acetonitrile at 120 °C for 24 h in a sealed tube.[21] However, the reaction of quinolin-2-one with substituted benzyl chloride derivatives in the presence of dichloro [9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene]palladium(II); potassium carbonate in toluene at 100 °C afforded either the O-substituted quinolone or a mixture of both O- and N-substituted quinolone derivatives.[22] Chemoselective reactions of heterocyclic amides with electrophiles were extensively investigated by our research group to afford either N-substituted, O-substituted, or a mixture of both. These results were used to structure and modify several heterocyclic systems and were supported by theoretical DFT calculations to predict the site of alkylation.[23−30] To find more promising quinoline derivatives for biological evaluation, we now report the preparation of *N*-alkyl-3-[2-oxoquinolin-1(2*H*)-yl]-propanamide and related compounds based on the chemoselective reaction of 2-quinolinone with methyl acrylate under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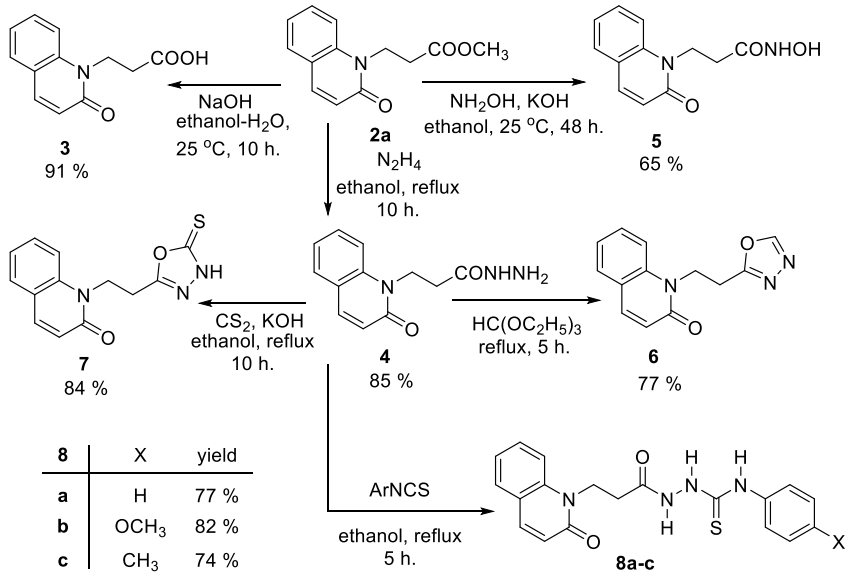
**Scheme 2. Chemistry of Methyl 3-[2-Oxoquinolin-1(2*H*)-yl]propanoate (2a) and 3-[2-Oxoquinolin-1(2*H*)-yl]propanhydrazide (3)**




| 8 | X | yield |
|---|---|---|
| a | H | 77 % |
| b | $OCH_3$ | 82 % |
| c | $CH_3$ | 74 % |

Michael reaction conditions and investigate their activity as cytotoxic agents, highlighting the effective molecular target.

## RESULTS AND DISCUSSION

2-Quinolinone (**1**) is an interesting ambident nucleophile consisting of a tautomeric mixture **1a** and **1b**, Scheme 1. Quinolin-2-one (**1**) reacts with activated olefins, ethyl acrylate, acrylonitrile, and acrylamide electrophile in the presence of potassium carbonate at 100 °C for 10 h and gives 3-[2-oxoquinolin-1-(2*H*)-yl] propanoic acid derivatives **2a−c** in 81−88% yield, Scheme 1. As far as our knowledge, no reaction was reported of quinolin-2-one with methyl acrylate, acrylonitrile, or activated double bond under Michael reaction condition to date.

The structure assignment of the acrylic acid derivatives **2a−c** was based on $^1$H and $^{13}$C NMR as well as physicochemical analysis. Thus, the $^1$H NMR spectrum of methyl 3-[2-oxoquinolin-1(2*H*)-yl]propanoate (**2a**) gave two triplet and a singlet signals $\delta$ 4.49, 2.67, and 3.61 ppm corresponding to $NCH_2$, $CH_2CO$, and $OCH_3$ groups, respectively. The $^{13}$C NMR spectrum of **2a** showed a signal at $\delta$ 38.2 ppm typically associated with N-substitution. The $^{13}$C NMR spectrum also shows signals at $\delta$ 32.2, 51.8, 161.9, and 171.5 ppm corresponding to $CH_2CO$, $OCH_3$, and two C═O groups, respectively.

The chemoselective reaction of amides with electrophiles is well-recognized in organic synthetic procedures. The ambident nucleophilic behavior of **1** toward electrophiles is dependent on several factors, including the structure of both nucleophiles and electrophiles, solvent, and base used. According to structure, the competition between O and N toward electrophiles is governed by Pearson HSAB theory, where soft electrophiles alkyl halides are oriented toward the soft part of the ambient nucleophile (N-atom). This is obvious from the results discussed earlier in the introduction part and in cases reported in the literature concerning the amide function group. The O-substitution is generally favored when we apply hard electrophiles. Indeed, there are some cases where both hard and soft features are aggregated on the oxygen atom, taking part in a continuous conjugation system, giving the O-substitution when reacting with both soft and hard electrophiles. We obtained O-substitution when amide 2-arylquinazolin-4(3*H*)-one reacts with both soft and hard electrophiles.[23,31] However, the N-substitution of **1** indicates that the N-atom is the harder part of the ambident nucleophile with a higher energy LUMO compared to oxygen. The reaction of 2-quinolinone (**1**) with acrylic acid derivatives seems rational, giving N-substitution; on the contrary, the reaction is unique. This leads us to more investigation related to other factors to fully understand this behavior.

Methyl 3-[2-oxoquinolin-1(2thyl 3-[2-oxoquinolin-1(2*H*)-yl]propanoate (**2a**) reacted with sodium hydroxide and hydrazine hydrate in ethanol, affording 3-[2-oxoquinolin-1(2*H*)-yl]propanoic acid (**3**) and 3-[2-oxoquinolin-1(2*H*)-yl]propanhydrazide (**4**) in 91% and 85% yields, respectively, Scheme 2. The ester **2a** and its corresponding carboxylic acid **3** and hydrazide **4** are interesting compounds used as building blocks to modify the structure of quinolone ring. This could be achieved by the attachment of organic residues with a variable range of lipophilicity and hydrophilicity to enhance the biological activity. Thus, the reaction of the ester **2a** with hydroxyl amine hydrochloride in the presence of potassium hydroxide in ethanol for 48 h afforded *N*-hydroxy-3-[2-oxoquinolin-1(2*H*)-yl]propanamide (**5**) in 65% yield, Scheme 2. The hydrazide **4** reacted either with triethyl orthoformate under reflux conditions for 5 h or with carbon disulfide in the presence of potassium hydroxide in ethanol under reflux condition for 10 h to afford oxadiazoles **6** and **7** in 77 and 84% yields, respectively, Scheme 2. The hydrazide **4** reacted with aryl isothiocyanates, phenyl isothiocyanate, *p*-anisyl isothiocyanate, and *p*-tolyl isothiocyanate in ethanol for 5 h under reflux condition and gave 4-aryl-1-{3-[2-oxoquinolin-1(2*H*)-yl]propanoyl} thiosemicarbazides **8a−c** in 77, 82, and 74% yields, respectively, Scheme 2.

Both carboxylic acid **3** and hydrazide **4** could be used for structure modification of quinolone through attachment of amine via dicyclohexyl carbodiimide (DCC) or azide coupling methods.[32,33] Multicomponent reactions are a well-recognized tool in organic synthesis. Thus, the 3-[2-oxoquinolin-1(2*H*)-yl]propanoic acid (**3**) reacted with amines—propyl amine,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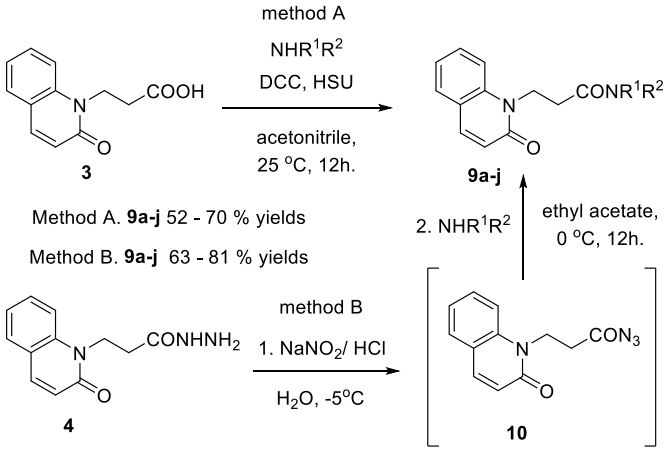
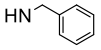
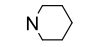
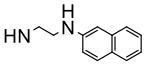
**Scheme 3. Preparation of *N*-Alkyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamides 9a−j**




| 9 | $NR^1R^2$ | Abbrev. | 9 | $NR^1R^2$ | Abbrev. | 9 | $NR^1R^2$ | Abbrev. |
|---|---|---|---|---|---|---|---|---|
| a | $NH(CH_2)_2CH_3$ | propyl amine | b | $NH(CH_2)_3CH_3$ | butyl amine | c | $NHCH(CH_3)_2$ | isopropyl amine |
| d | $NHCH_2CH{=}CH_2$ | allyl amine | e |  | benzyl amine | f |  | cyclohexyl amine |
| g |  | morpholine | h |  | piperidine | i |  | pyrrolidine |
| j |  | β-naphthalene ethylenediamine | | | | | | |

butyl amine, isopropyl amine, allyl amine, benzylamine, cyclohexyl amine, morpholine, piperidine, pyrrolidine, and *β*-naphthylethylene diamine—in the presence of hydroxysuccinimide (HSU) and DCC at room temperature to give *N*-alkyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamides **9a−j** in 49−70% yields via DCC coupling method following the multicomponent strategy, Scheme 3.

The azide coupling method is an excellent method used to attach amines via peptide bond from corresponding hydrazides with one pot, low temperature, simple workup, gas byproducts, and high yield advantages. The hydrazide reacted with sodium nitrite at −5 °C for 0.5 h to give the in situ generated, which further reacted with amines—propyl amine, butyl amine, isopropyl amine, allyl amine, benzylamine, cyclohexyl amine, morpholine, piperidine, pyrrolidine, and *β*-naphthylethylenediamine—in a one-pot strategy to afford *N*-alkyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamides **9a−j** in 63−81% yields. The azide coupling method gave the corresponding amides **9a−j** with a relatively higher yield than the DCC coupling method and at a lower temperature, as shown in Scheme 3.

The structure assignment of 3-[2-oxoquinolin-1(2*H*)-yl]-propanoic acid (**3**), 3-[2-oxoquinolin-1(2*H*)-yl]-propanehydrazide (**4**), oxadiazoles **6**, **7**, thiosemicarbazides **8a−c**, and *N*-alkyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamides **9a−j** was based on $^1$H and $^{13}$C NMR as well as physicochemical analysis. The $^1$H NMR spectrum of *N*-isopropyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamide (**9c**) showed two triplet signals at *δ* 2.60 and 4.55 ppm associated with $CH_2CO$ and $NCH_2$ groups, respectively, Figure 2. The $^1$H NMR spectrum of **9c** also shows signals at *δ* 6.66, 1.06, and 3.98−403 ppm corresponding to NH, $CH_3$ CH of the isopropyl amine residue. The $^{13}$C NMR spectrum of **9c** shows signals at *δ* 22.6, 32.4, 38.6, 43.8, 166.5, and 172.7 ppm

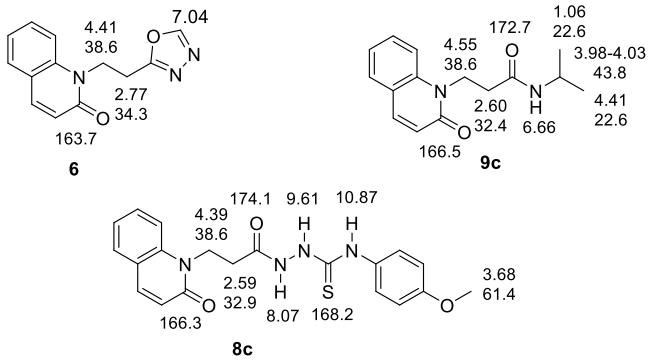



**Figure 2.** Selected signals for the $^1$H and $^{13}$C NMR spectra of 1-[2-(1,3,4-oxadiazol-2-yl)ethyl]quinolin-2(1*H*)-one (**6**), 4-(4-methoxyphenyl)-1-{3-[2-oxoquinolin-1(2*H*)-yl]propanoyl}thiosemicarbazide (**8c**), and *N*-isopropyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamide (**9c**).

corresponding to $CH_3$, $CH_2CO$, $NCH_2$, NCH, C═O quinolone, and C═O amide, respectively, Figure 2.

All synthesized compounds were screened for the binding affinity toward the epidermal growth factor receptor (EGFR) target protein using the molecular docking study by interpreting both binding energy and binding interactions with the key amino acids. As seen in the Supplementary file (Table S1), interestingly, compounds **9c**, **9d**, **9e**, and **9g** exhibited the highest binding energy ranging from −19.8 to −24.8 kcal/mol, forming interactions with the key amino acid, Met 769. Other compounds exhibited a moderate binding affinity. Hence, these compounds are worthy of being further investigated with both cell-based and molecular target assays to investigate their activity as anticancer agents.



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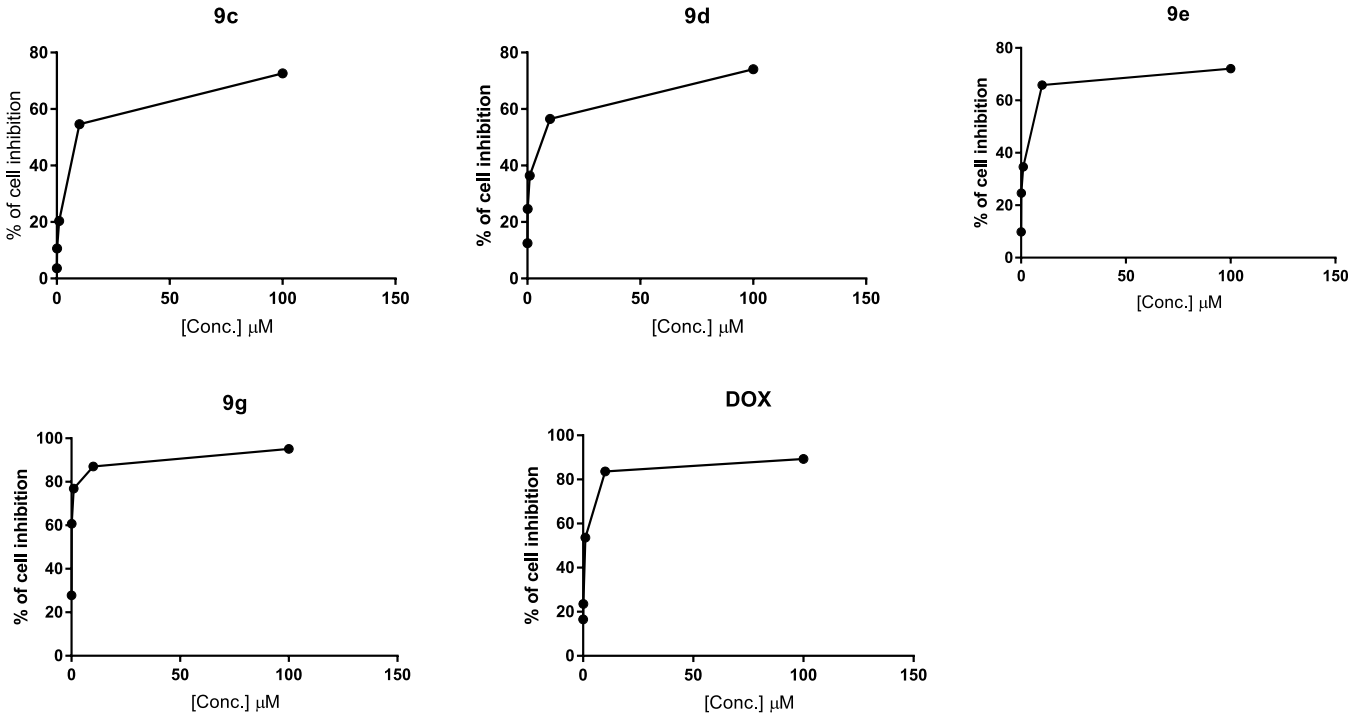


**Figure 3.** Cell growth inhibition versus log concentrations of compounds **9c**, **9d**, **9e**, and **9g** cells using the MTT assay. Values are expressed as mean ± SD of three independent values.

## BIOLOGICAL INVESTIGATION

**Cytotoxicity against MCF-7 Cells.** Using the MTT assay, the cytotoxic activity of the synthesized compounds was investigated against breast (MCF-7) cancer cells (Figure 3). As summarized in Table 1 with the $IC_{50}$ values, the cytotoxic effects of compounds **9c**, **9d**, **9e**, and **9g** were much stronger than those of doxorubicin ($IC_{50}$ = 1.21 μM), with $IC_{50}$ values of 2.32, 4.68, 1.32, and 9.77 μM, respectively. Therefore, it would have been worthwhile to examine these drugs for an efficient molecular target that initiated the cytotoxicity.

**Table 1. Cytotoxicity of the Synthesized Derivatives against MCF-7 Cells Using the MTT Assay**

| compounds | % of cell growth inhibition at [100 μM] | IC50 (μM) ± SD[a] |
|---|---|---|
| **9c** | 92.3 | 2.32 ± 0.2 |
| **9d** | 91.36 | 4.68 ± 1.5 |
| **9e** | 97.5 | 1.32 ± 1.9 |
| **9g** | 90.47 | 9.77 ± 0.9 |
| **doxorubicin** | 96.8 | 1.21 ± 0.03 |

[a]"$IC_{50}$ values were calculated as the average of three independent trials using a dose−response curve in GraphPad prism". NT = not tested.

These cytotoxicity results agreed with previously published ones of being promising candidates for further development as antibreast cancer agents. The study demonstrated that oxoquinoline is a crucial pharmacophoric moiety for anticancer treatment research since several quinoline-based derivatives exhibited promising $IC_{50}$ values against a panel of cancer cell lines.

**EGFR Enzyme Inhibition.** A luminescent test kit was used to measure the percentage of enzyme inhibition at different doses for EGFR, a kind of tyrosine kinase receptor. Compounds **9c**, **9d**, **9e**, and **9g** were tested for EGFR inhibition, as seen in Table 2. They had promising EGFR2 inhibition percentages of 95.7, 89.8, 97.0, and 86.8% with $IC_{50}$ values of 27.9, 30.4, 16.89, and 52.7 nM, respectively, compared to Erlotinib with 96.8% and an $IC_{50}$ value of 20.8 nM. Hence, compound **9e** exhibited potent cytotoxicity against MCF-7 cells with EGFR inhibition compared to Erlotinib.

**Table 2. Percentage of EGFR Inhibition with $IC_{50}$ Values for the Most Cytotoxic Compounds**

| | EGFR | |
|---|---|---|
| compound | % of inhibition at [10 μM] | $IC_{50}$ [nM] ± SD[a] |
| **9c** | 95.7 ± 1.6 | 27.9 ± 1.4 |
| **9d** | 89.8 ± 1.9 | 30.4 ± 1.3 |
| **9e** | 97.0 ± 2.3 | 16.89 ± 0.6 |
| **9g** | 86.8 ± 2.4 | 52.7 ± 1.9 |
| **Erlotinib** | 96.8 ± 3.4 | 20.8 ± 0.8 |

[a]"Values are expressed as an average of three independent replicates." "$IC_{50}$ values were calculated using sigmoidal nonlinear regression curve fit of percentage inhibition against five concentrations of each compound."

These results of cytotoxicity and EGFR inhibition corroborated those of earlier research[12−15] that has shown that studying quinoline nuclei is an exciting new avenue for the discovery of cancer-fighting medicines, pharmacophores, and hybrids. Quinoline hybrids have demonstrated promising results with novel targets that work in a distinct way to limit cell proliferation through cell cycle arrest, apoptosis, angiogenesis, cell migration disruption, and regulation. This highlighted the molecular docking, structure−activity connection, and mechanism of action of quinoline hybrids, which are responsible for their new anticancer properties. So, to cure


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certain disorders, several quinoline candidates are now being tested in clinical studies.

**Molecular Docking Studies.** The ability of oxoquinolines to suppress kinase activity makes them attractive anticancer medicines. Reportedly, they may inhibit protein kinase phosphorylation reactions and the signaling pathways that lead to them, making them a promising scaffold for anticancer medicines.[31−33]

A structural bioinformatics technique called molecular docking was used to learn more about the interaction between drugs and proteins as well as the locations of their active sites. A molecular docking research was conducted on compound **9e** to reveal its virtual binding mechanism to the EGFR protein. As seen in Figure 4, it maintained the binding mode of the

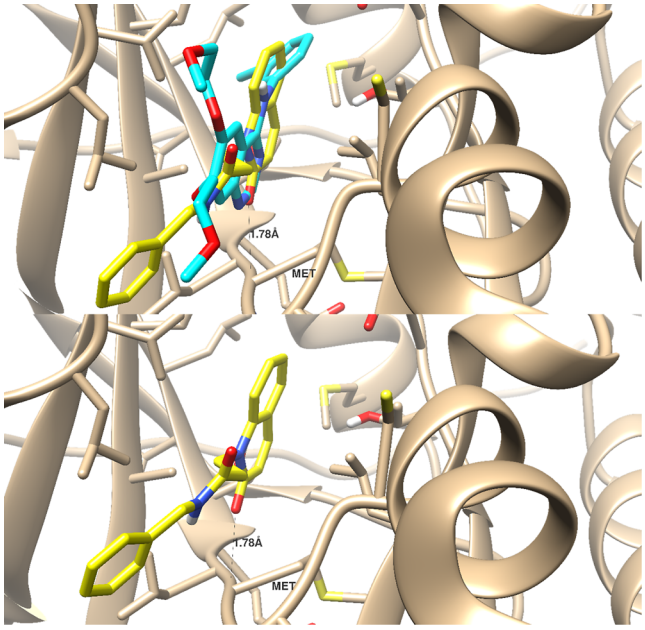


**Figure 4.** Binding mode and ligand−receptor interactions of the cocrystallized ligand (cyan-colored) and compound **9e** (yellow-colored) inside the receptor binding site of EGFR protein.

cocrystallized ligand; it was docked inside the EGFR binding site with a binding energy of −21.6 kcal/mol, it formed H-bond interaction with Met 769 with a bond length of 1.78 A, and it connected with the nonpolar amino acids within the protein active site through lipophilic interactions.

## EXPERIMENTAL SECTION

**Preparation of 3-[2-Oxoquinolin-1(2*H*)-yl]propanoic Acid Derivatives 2a−c.** A mixture of 2-quinolinone (**1**) (1.45 g, 10 mmol), potassium carbonate (1.38 g, 10.0 mmol), and acrylic acid derivatives (40.0 mmol) (ethyl acrylate, acrylamide, and acrylonitrile) was heated in an oil bath for 10 h at 100 °C (TLC monitored) The reaction mixture was cooled, evaporated under reduced pressure and was dissolved in ethyl acetate, washed several times with water, and dried over sodium sulfate. The ethyl acetate solution was evaporated under reduced pressure, and the resultant product was crystallized from ethanol.

**Methyl 3-[2-Oxoquinolin-1(2*H*)-yl]propanoate (2a).** White crystals, yield 88%. mp 141−142 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 2.67 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 3.61 (s, 3H, $OCH_3$), 4.49 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 6.57 (d, *J* = 9.0 Hz, 1H, CH), 7.11−7.22 (m, 1H, Ar−H), 7.31−7.49 (m, 3H, Ar−H), 7.59 (d, *J* = 9.0 Hz, 1H, CH). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 32.2 ($CH_2CO$), 38.2 ($NCH_2$), 51.8 ($OCH_3$), 113.7, 119.2, 125.2, 129.1, 130.8, 133.0, 136.5, 138.9 (C−Ar), 161.9, 171.5 (2 CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 254.27 $(M + Na)^+$. Anal. Calcd for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.56; H, 5.71; N, 6.10.

**3-[2-Oxoquinolin-1(2*H*)-yl]propanamide (2b).** White crystals, yield 87%. mp 157−158 °C. $^1$H NMR spectrum, (400 MHz, DMSO): *δ*, ppm (*J*, Hz): 2.54 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 3.66 (br s, 2H, $NH_2$), 4.41 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.10−7.19 (m, 2H, Ar−H), 7.31−7.47 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, DMSO): *δ*, ppm: 32.9, 38.3, 118.3, 121.4, 122.6, 125.8, 126.5, 127.3, 133.5, 137.4 (C−Ar), 166.7, 173.2 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 239.26 $(M + Na)^+$. Anal. Calcd for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.69; H, 5.64; N, 13.02.

**3-[2-Oxoquinolin-1(2*H*)-yl]propanonitrile (2c).** White crystals, yield 81%. mp 136−137 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 2.67 (t, *J* = 8.0 Hz, 2H, $CH_2CN$), 4.49 (t, *J* = 8.0 Hz, 2H, $NCH_2$), 6.58 (d, *J* = 8.2 Hz, 1H, Ar−H), 7.13 (t, *J* = 8.2 Hz, 1H, Ar−H), 7.33−7.52(m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 18.4, 38.2, 113.7, 118.6, 120.9, 121.5, 122.2, 126.3, 129.3, 130.8, 138.8, 139.3 (C−Ar), 161.9, (CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 221.24 $(M + Na)^+$. Anal. Calcd for $C_{12}H_{10}N_2O$ (198.23): C, 72.71; H, 5.08; N, 14.13. Found: C, 72.76; H, 5.13; N, 14.17.

**Preparation of 3-[2-Oxoquinolin-1(2*H*)-yl]propanoic Acid (3).** To a solution of ethyl 3-[2-oxoquinolin-1(2*H*)-yl]propanoate (**2a**) (2.45 g, 10 mmol) in 15 mL of ethyl alcohol was added sodium hydroxide (0.4 g, 10 mmol) solution in 15 mL of water, and the reaction mixture was heated at 25 °C for 10 h (TLC monitored until complete consumption of the ester). The reaction mixture was filtered, cooled, and acidified with acetic acid. The crude product was filtered, dried, and crystallized from ethanol.

White crystals, yield 91%. mp 181−183 °C. $^1$H NMR spectrum, (400 MHz, DMSO): *δ*, ppm (*J*, Hz): 2.63 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 4.42 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.11−7.18 (m, 2H, Ar−H), 7.32−7.49 (m, 4H, Ar−H), 10.12 (br s, 1H, COOH). $^{13}$C NMR (100.0 MHz, DMSO): *δ*, ppm: 32.8, 38.4, 118.1, 121.2, 122.4, 125.5, 126.7, 127.1, 133.4, 137.3 (C−Ar), 166.5, 172.8 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 240.24 $(M + Na)^+$. Anal. Calcd for $C_{12}H_{11}NO_3$ (217.22): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.39; H, 5.14; N, 6.49.

**Preparation of 3-[2-Oxoquinolin-1(2*H*)-yl]-propanehydrazide (4).** A mixture of *N*-substituted quinolone **2a** (2.45 g, 10 mmol) and hydrazine hydrate (1.0 mL, 20 mmol) was dissolved in ethanol 95% (20 mL) and was refluxed at 78 °C for 10 h (TLC monitored until consumption of ester). The reaction mixture was concentrated under reduced pressure, cooled, and the resultant crystals were filtered off. The obtained solid was crystallized with ethanol to give the pure hydrazide **4**.

White crystals, yield 85%. mp 188−190 °C. $^1$H NMR spectrum, (400 MHz, DMSO): *δ*, ppm (*J*, Hz): 2.62 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 3.45−3.51 (m, 2H, $NH_2$), 4.43 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.13−7.26 (m, 2H, Ar−H), 7.33−7.52 (m, 4H, Ar−H), 9.11 (br s, 1H, NH). $^{13}$C NMR (100.0 MHz,


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DMSO): δ; ppm: 32.5, 38.7, 118.0, 121.6, 122.2, 125.5, 126.0, 127.4, 133.6, 137.1 (C−Ar), 166.2, 172.4 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 254.12 (M + Na)$^+$. Anal. Calcd for $C_{12}H_{13}N_3O_2$ (231.26): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.41; H, 5.73; N, 18.20.

**Preparation of *N*-Hydroxy-3-[2-oxoquinolin-1(2*H*)-yl]propanamide (5).** A solution of methyl 3-[2-oxoquinolin-1(2*H*)-yl]propanoate (**2a**) (2.31 g, 1.0 mmol) and potassium hydroxide (0.56 g, 10 mmol) in 30 mL of ethanol was stirred at room temperature for 15 min. To this solution, hydroxyl amine hydrochloride (0.65 g, 10 mmol) was added, and the reaction mixture was stirred at room temperature for 48 h (TLC monitored until consumption of ester **2a**). The reaction mixture was evaporated under reduced pressure dissolved in ethyl acetate, washed with water, and dried over sodium sulfate. The ethyl acetate solution was evaporated under reduced pressure, and the resultant crude *N*-hydroxy-3-[2-oxoquinolin-1(2*H*)-yl]propanamide (**5**) was crystallized from ethanol.

White crystals, yield 65%. mp 188−190 °C. $^1$H NMR spectrum, (400 MHz, DMSO): δ, ppm (*J*, Hz): 2.62 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 4.43 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.13−7.26 (m, 2H, Ar−H), 7.33−7.52 (m, 4H, Ar−H), 9.11 (br s, 1H, NH), 10.18 (br s, 1H, OH). $^{13}$C NMR (100.0 MHz, DMSO): δ, ppm: 32.2, 38.3, 118.2, 121.4, 122.1, 125.3, 126.2, 127.5, 133.6, 137.1 (C−Ar), 166.3, 169.1 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 255.26 (M + Na)$^+$. Anal. Calcd for $C_{12}H_{12}N_2O_3$ (232.24): C, 62.06; H, 5.21; N, 12.06. Found: C, 62.11; H, 5.24; N, 12.10.

**Preparation of 1-[2-(1,3,4-Oxadiazol-2-yl)ethyl]-quinolin-2(1*H*)-one (6).** A mixture of 3-[2-oxoquinolin-1(2*H*)-yl]propanehydrazide (**4**) (0.23 g, 1.0 mmol), triethyl orthoformate (12 mmol), and two drops of acetic acid was heated at 104 °C for 5 h (TLC monitored). The reaction mixture was cooled to give crystals, filtered, and crystallized with acetic acid.

Yellow crystals, yield 77%. mp 141−142 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): δ, ppm (*J*, Hz): 2.67 (t, *J* = 8.0 Hz, 2H, $CH_2$), 4.49 (t, *J* = 8.0 Hz, 2H, $NCH_2$), 6.58 (d, 1H, *J* = 8.2 Hz, AR-H), 7.01 (s, 1H, N═CH), 7.11−7.20 (t, 1H, *J* = 8.0 Hz, Ar−H), 7.32−7.52 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): δ, ppm: 34.3, 38.6, 118.1, 121.5, 122.4, 125.8, 126.3, 127.4, 133.6, 137.3, 155.4 (C═N), 161.9 (C═O), 163.6 (C═N). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 264.27 (M + Na)$^+$. Anal. Calcd for $C_{13}H_{11}N_3O_2$ (241.25): C, 64.72; H, 4.60; N, 17.42. Found: C, 64.76; H, 4.64; N, 17.47.

**Preparation of 1-[2-(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)ethyl]quinolin-2(1*H*)-one (7).** A solution of 3-[2-oxoquinolin-1(2*H*)-yl]propanehydrazide (**4**) (2.31 g, 10.0 mmol) in ethanol (30 mL) was added to potassium hydroxide (0.56 g, 10 mmol) and carbon disulfide (1.42 mL, 20.0 mmol). The reaction mixture was refluxed for 10 h, then cooled and acidified with 1 M HCl. The resultant yellowish precipitate was filtered off, washed with water, and dried. The crude oxadiazole **7** was crystallized from DMF.

Yellow crystals, yield 84%. mp 156−157 °C. $^1$H NMR spectrum, (400 MHz, DMSO): δ, ppm (*J*, Hz): 2.81 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 4.37 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.10−7.18 (m, 2H, Ar−H), 7.30−7.48 (m, 4H, Ar−H), 9.02 (s, 1H, NH). $^{13}$C NMR (100.0 MHz, $CDCl_3$): δ, ppm: 33.8, 38.3, 118.3, 121.6, 122.2, 125.7, 126.5, 127.3, 133.4, 137.6 (C−Ar), 154.7 (C═N), 166.5 (CO), 171.3 (C═S). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 269.33 (M + Na)$^+$. Anal. Calcd for $C_{13}H_{11}N_3O_2S$ (273.31): C, 57.13; H, 4.06; N, 15.37. Found: C, 57.17; H, 4.10; N, 15.41.

**Preparation of 4-Aryl-1-{3-[2-oxoquinolin-1(2*H*)-yl]-propanoyl}thiosemicarbazides 8a−c.** To a solution of 3-[2-oxoquinolin-1(2*H*)-yl]propanehydrazide (**4**) (2.31 g, 10.0 mmol) in 30 mL ethanol were added aryl isothiocyanates—phenyl isothiocyanate, *p*-anisyl isothiocyanate, and *p*-tolyl isothiocyanate. The reaction mixture was refluxed for 5 h (TLC monitored), cooled, and the resultant crystals were filtered off. The crude thiosemicarbazides **8a−c** were crystallized from DMF.

**1-{3-[2-Oxoquinolin-1(2*H*)-yl]propanoyl}-4-phenyl Thiosemicarbazide (8a).** White crystals, yield 77%. mp 161−163 °C. $^1$H NMR spectrum, (400 MHz, DMSO): δ, ppm (*J*, Hz): 2.64 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 4.43 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.09−7.20 (m, 2H, Ar−H), 7.28−7.44 (m, 7H, Ar−H), 7.57−7.71 (m, 2H, Ar−H), 8.18 (br s, 1H, NH), 9.67 (br s, 1H, NH), 10.92 (br s, 1H, NH). $^{13}$C NMR (100.0 MHz, DMSO): δ, ppm: 32.9, 38.7, 118.4, 121.2, 122.5, 125.4, 125.9, 126.2, 126.5, 127.1, 127.4, 133.3, 136.7, 137.6, 165.7, 168.5 (2CO), 174.4 (C═S). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 389.46 (M + Na)$^+$. Anal. Calcd for $C_{19}H_{18}N_4O_2S$ (366.44): C, 62.28; H, 4.95; N, 15.29. Found: C, 62.32; H, 4.98; N, 15.33.

**4-(4-Methoxyphenyl)-1-{3-[2-oxoquinolin-1(2*H*)-yl]-propanoyl}thiosemicarbazide (8b).** White crystals, yield 82%. mp 154−155 °C. $^1$H NMR spectrum, (400 MHz, DMSO): δ, ppm (*J*, Hz): 2.59 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 3.68 (s, 3H, OMe), 4.39 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.12−7.21 (m, 2H, Ar−H), 7.28−7.44 (m, 6H, Ar−H), 7.51−7.66 (m, 2H, Ar−H), 8.07 (br s, 1H, NH), 9.61 (br s, 1H, NH), 10.87 (br s, 1H, NH). $^{13}$C NMR (100.0 MHz, DMSO): δ, ppm: 32.9, 38.6, 61.4, 118.2, 121.5, 122.7, 125.4, 125.8, 126.6, 126.8, 127.4, 127.6, 133.2, 136.6, 157.4, 166.3, 168.2 (2CO), 174.1 (C═S). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 419.49 (M + Na)$^+$. Anal. Calcd for $C_{20}H_{20}N_4O_3S$ (396.47): C, 60.59; H, 5.08; N, 14.13. Found: C, 60.64; H, 5.13; N, 14.18.

**1-{3-[2-Oxoquinolin-1(2*H*)-yl]propanoyl}-4-(4-tolyl)-thiosemicarbazide (8c).** White crystals, yield 74%. mp 148−150 °C. $^1$H NMR spectrum, (400 MHz, DMSO): δ, ppm (*J*, Hz): 2.11 (s, 3H, $CH_3$), 2.54 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 4.36 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.10−7.22 (m, 2H, Ar−H), 7.29−7.41 (m, 6H, Ar−H), 7.47−7.54 (m, 2H, Ar−H), 8.12 (br s, 1H, NH), 9.65 (br s, 1H, NH), 10.91 (br s, 1H, NH). $^{13}$C NMR (100.0 MHz, DMSO): δ; ppm: 21.4, 32.3, 38.2, 118.1, 121.3, 122.5, 125.2, 125.7, 126.4, 126.7, 127.5, 127.8, 133.4, 136.8, 137.3, 166.5, 168.3 (2CO), 174.4 (C═S). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 403.49 (M + Na)$^+$. Anal. Calcd for $C_{20}H_{20}N_4O_2S$ (380.47): C, 63.14; H, 5.30; N, 14.73. Found: C, 63.14; H, 5.30; N, 14.73.

**Preparation of *N*-Alkyl-3-[2-oxoquinolin-1(2*H*)-yl]-propanamides 9a−j.** *Method A (DCC Coupling).* 3-[2-Oxoquinolin-1(2*H*)-yl]propanoic acid (**3**) (2.17 g, 10 mmol) was dissolved in 25 mL of dry acetonitrile. To this solution were added *N*-hydroxysuccinimide (NHS) (1.12 g, 10.0 mmol), DCC (2.20 g, 10.0 mmol), and amines—propyl amine, butyl amine, isopropyl amine, allyl amine, benzylamine, cyclohexyl amine, morpholine, piperidine, pyrrolidine, and β-naphthylethylenediamine (10.0 mmol). The reaction mixture was stirred at 0 °C for 2 h and at RT for 12 h. The resultant precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The oily residue was dissolved in ethyl


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acetate and once again filtered off. This previous step was repeated 3 times to remove all the dicyclohexyl urea byproduct. The ethyl acetate solution was washed with 1 M of sodium carbonate, 1 M HCl, and water and was dried over sodium sulfate. The ethyl acetate solution was dried over sodium sulfate and then evaporated and crystallized from ethyl acetate petroleum ether to give *N*-alkyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamides **9a**−**j**.

*Method B (Azide Coupling).* A cold solution of $NaNO_2$ (0.34 g, 5.0 mmol) in cold water (3 mL) was added to a cold solution (−5 °C) of 3-[2-oxoquinolin-1(2*H*)-yl]-propanehydrazide (**4**) (0.23 g, 1.0 mmol) in AcOH (6 mL), 1 N HCl (3 mL), and water (25 mL). After stirring at −5 °C for 30 min, the reaction mixture was extracted with ethyl acetate, washed with 0.5 N HCl (30 mL), 3% $NaHCO_3$ (30 mL), and $H_2O$ (30 mL), and finally dried over $Na_2SO_4$ (10 g) to give an ethyl acetate solution of azide **10**. A solution of appropriate amines (1.0 mmol)—propyl amine, butyl amine, isopropyl amine, allyl amine, benzyl amine, cyclohexyl amine, pyrrolidine, and piperidine in ethyl acetate—was added to the solution of azide **10**. The mixture was kept at −5 °C for 24 h, then at 25 °C for another 24 h, followed by washing with 0.5 N HCl (30 mL), 3% $NaHCO_3$ (30 mL), and $H_2O$ (30 mL), and finally dried over $Na_2SO_4$ (10 g). The solution was evaporated to dryness, and the residue was recrystallized from petroleum ether/ethyl acetate, 1:3, to give the desired product **9a**−**j**.

***N*-Propyl-3-[2-oxoquinolin-1(2*H*)-yl] Propanamide (9a).** From propyl amine, white crystals, method A yield 58%. Method B yield 71%. mp 134−135 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 0.74−0.84 (m, 3H, $CH_3$), 1.33−1.48 (m, 2H, $CH_2$), 2.56 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 3.02−3.09 (m, 2H, $NHCH_2$), 4.46 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 6.88 (br s, 1H, NH), 7.09−7.13 (m, 2H, Ar−H), 7.39−7.46 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 11.5 ($CH_3$), 22.7 ($CH_2$), 32.4 ($CH_2CO$), 38.5 ($NCH_2$), 42.3 ($NCH_2$), 118.2, 121.5, 122.4, 125.6, 126.1, 127.4, 133.1, 137.4, 166.2, 172.7 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 281.34 $(M + Na)^+$. Anal. Calcd. for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.81; H, 7.10; N, 10.92.

***N*-Butyl-3-[2-oxoquinolin-1(2*H*)-yl]propanamide (9b).** From butyl amine, white crystals, method A yield 61%. Method B yield 77%. mp 127−129 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 0.99−1.02 (m, 3H, $CH_3$), 1.02−1.28 (m, 4H, 2 $CH_2$), 2.44 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 2.90−2.97 (m, 2H, $NHCH_2$), 4.31 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 6.93−6.97 (m, 2H, Ar−H), 7.19 (br s, 1H, NH), 7.26−7.39 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 13.6 ($CH_3$), 20.1 ($CH_2$), 23.2 ($CH_2$), 32.1 ($CH_2CO$), 38.5 ($NCH_2$), 42.7 ($NCH_2$), 118.0, 121.3, 122.5, 125.4, 126.2, 127.5, 133.3, 137.2, 166.4, 172.6 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 295.37 $(M + Na)^+$. Anal. Calcd for $C_{16}H_{20}N_2O_2$ (272.35): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.62; H, 7.51; N, 10.36.

***N*-Isopropyl-3-[2-oxoquinolin-1(2*H*)-yl] Propanamide (9c).** From isopropyl amine, white crystals, method A yield 56%. Method B yield 67%. mp 124−125 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 1.06 (d, *J* = 3.0 Hz. Six H, 2 $CH_3$), 2.60 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 3.98−4.03 (m, 1H, NHCH), 4.55 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 6.66 (br s, 1H, NH), 7.16−7.20 (m, 2H, Ar−H), 7.50−7.61 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 22.6 (2 $CH_3$), 32.4 ($CH_2CO$), 38.6 ($NCH_2$), 43.8 (NCH), 118.3, 121.5, 122.4, 125.2, 126.4, 127.3, 133.5, 137.1, 166.5, 172.7 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 281.16 $(M + Na)^+$. Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.32): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.81; H, 7.11; N, 10.92.

***N*-Allyl-3-[2-oxoquinolin-1(2*H*)-yl] Propanamide (9d).** From allyl amine, white crystals, method A yield 53%. Method B yield 76%. mp 119−121 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 2.66 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 4.34 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 4.43−4.50 (m, 2H, $NHCH_2$), 4.53−5.03 (m, 1H, CH), 5.05−5.17 (m, 1H, CH), 5.69−5.81 (m, 1H, CH), 7.15−7.22 (m, 2H, Ar−H), 7.28 (br s, 1H, NH), 7.45−7.59 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 32.3 ($CH_2CO$), 38.2 ($NCH_2$), 43.0 ($NCH_2$), 116.7, 118.6, 121.4, 122.2, 125.6, 126.5, 127.6, 133.2, 135.4, 137.3, 166.5, 172.2 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 279.33 $(M + Na)^+$. Anal. Calcd for $C_{15}H_{16}N_2O_2$ (256.31): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.36; H, 6.34; N, 10.98.

***N*-Benzyl-3-[2-oxoquinolin-1(2*H*)-yl] Propanamide (9e).** From benzyl amine, white crystals, method A yield 64%. Method B yield 81%. mp 139−140 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 2.65 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 4.31−4.35 (m, 2H, $CH_2$ ph), 4.56 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 6.85 (br s, 1H, NH), 7.14−7.34 (m, 7H, Ar−H), 7.36−7.55 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 32.1 ($CH_2CO$), 38.5 ($NCH_2$), 41.7 ($CH_2Ph$), 118.2, 121.5, 122.2, 125.4, 126.3, 127.5, 128.4, 128.6, 129.8, 133.4, 135.5, 137.4, 166.7, 172.3 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 329.39 $(M + Na)^+$. Anal. Calcd for $C_{19}H_{18}N_2O_2$ (306.37): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.54; H, 5.99; N, 9.21.

***N*-Cyclohexyl-3-[2-oxoquinolin-1(2*H*)-yl] Propanamide (9f).** From cyclohexyl amine, white crystals, method A yield 52%. Method B yield 66%. mp 137−139 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 1.03−1.12 (m, 4H, 2 $CH_2$), 1.18−1.31 (m, 2H, $CH_2$), 1.51−1.60 (m, 2H, $CH_2$), 1.63−1.79 (m, 2H, $CH_2$), 2.60 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 3.65−3.72 (m, 1H, NHCH), 4.54 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 6.68 (br s, 1H, NH), 7.14−7.18 (t, *J* = 6.0 Hz, 2H, Ar−H), 7.43−7.67 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 24.6 (2 $CH_2$), 25.5 ($CH_2$), 31.7 (2 $CH_2$), 32.5 ($CH_2CO$), 38.4 ($NCH_2$), 44.7 (NHCH), 118.4, 121.3, 122.5, 125.3, 127.7, 133.1, 135.3, 137.6, 166.4, 172.2 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 321.41 $(M + Na)^+$. Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.39): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.54; H, 7.48; N, 9.42.

**1-(3-Morpholino-3-oxopropyl)quinolin-2(1*H*)-one (9g).** From morpholine, white crystals, method A yield 70%. Method B yield 67%. mp 143−144 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 2.69 (t, *J* = 6.0 Hz, 2H, $CH_2CO$), 3.38−3.51 (m, 4H, 2 $CH_2N$), 3.70−3.83 (m, 4H, 2 $CH_2O$), 4.50 (t, *J* = 6.0 Hz, 2H, $NCH_2$), 7.13−7.26 (m, 2H, Ar−H), 7.44−7.57 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): *δ*, ppm: 32.3 ($CH_2CO$), 38.1 ($NCH_2$), 46.5 ($NCH_2$), 46.8 ($NCH_2$), 66.5 ($OCH_2$), 66.7 ($OCH_2$), 118.3, 121.2, 122.4, 125.5, 127.7, 133.2, 135.6, 137.3, 166.2, 172.5 (2CO). MS (MALDI, positive mode, matrix DHB) *m*/*z*: 309.35 $(M + Na)^+$. Anal. Calcd for $C_{16}H_{18}N_2O_3$ (286.33): C, 67.12; H, 6.34; N, 9.78. Found: C, 67.18; H, 6.40; N, 9.86.

**1-[3-Oxo-3-(piperidin-1-yl)propyl]quinolin-2(1*H*)-one (9h).** From piperidine, white crystals, method A yield 54%. Method B yield 72%. mp 137−138 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): *δ*, ppm (*J*, Hz): 1.39−1.50 (m, 6H, 3


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$CH_2$), 2.67 (t, $J$ = 6.0 Hz, 2H, $CH_2CO$), 3.27−3.45 (m, 4H, 2 $NCH_2$), 4.49 (t, $J$ = 6.0 Hz, 2H, $NCH_2$), 7.10−7.13 (m, 2H, Ar−H), 7.41−7.50 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): $\delta$, ppm: 25.4 ($CH_2$), 26.3 ($CH_2$), 28.8 ($CH_2$), 32.4 ($CH_2CO$), 38.4 ($NCH_2$), 43.6 ($2NCH_2$), 118.2, 121.1, 122.5, 125.2, 127.6, 133.2, 135.7, 137.4, 166.2, 172.1 (2CO). MS (MALDI, positive mode, matrix DHB) $m/z$: 307.38 $(M + Na)^+$. Anal. Calcd for $C_{17}H_{20}N_2O_2$ (284.36): C, 71.81; H, 7.09; N, 9.85. Found: C, 71.86; H, 7.13; N, 9.93.

**1-[3-Oxo-3-(pyrrolidin-1-yl)propyl]quinolin-2(1*H*)-one (9i).** From pyrrolidine, white crystals, method A yield 52%. Method B yield 69%. mp 127−128 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): $\delta$, ppm ($J$, Hz): 1.76−1.94 (m, 4H, 2 $CH_2$), 2.62 (t, $J$ = 6.0 Hz, 2H, $CH_2CO$), 3.28−3.47 (m, 2H, $NCH_2$), 4.44 (t, $J$ = 6.0 Hz, 2H, $NCH_2$), 7.11−7.17 (m, 2H, Ar−H), 7.45−7.52 (m, 4H, Ar−H). $^{13}$C NMR (100.0 MHz, $CDCl_3$): $\delta$, ppm: 24.5 ($CH_2$), 26.1 ($CH_2$), 32.2 ($CH_2CO$), 38.1 ($NCH_2$), 44.0 ($2NCH_2$), 118.0, 121.2, 122.3, 125.4, 127.5, 133.4, 135.6, 137.2, 166.3, 172.2 (2CO). MS (MALDI, positive mode, matrix DHB) $m/z$: 293.35 $(M + Na)^+$. Anal. Calcd for $C_{16}H_{16}N_2O_2$ (270.33): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.16; H, 6.75; N, 10.41.

***N*-[2-(Naphthalen-2-ylamino)ethyl]-3-[2-oxoquinolin-1(2*H*)-yl] Propanamide (9j).** From naphthalene ethylenediamine, white crystals, method A yield 54%. Method B yield 63%. mp 128−130 °C. $^1$H NMR spectrum, (400 MHz, $CDCl_3$): $\delta$, ppm ($J$, Hz): 2.64 (t, $J$ = 6.0 Hz, 2H, $CH_2CO$), 3.82 (m, 2H, $HNCH_2$), 3.90 (m, 2H, $HNCH_2$), 4.51 (t, $J$ = 6.0 Hz, 2H, $NCH_2$), 6.83 (br s, 1H, NH), 7.11−7.24 (m, 6H, Ar−H), 7.32−7.44 (m, 4H, Ar−H), 7.52−7.61 (m, 3H, Ar−H), 8.72 (br s, 1H, NH). $^{13}$C NMR (100.0 MHz, $CDCl_3$): $\delta$, ppm: 32.7 ($CH_2CO$), 38.9 ($NCH_2$), 43.2 ($NCH_2$), 44.5 ($NCH_2$), 118.1, 121.7, 122.4, 124.3, 125.3, 125.8, 126.5, 127.3, 127.8, 128.2, 128.6, 129.4, 133.3, 135.7, 137.2, 139.3, 166.8, 171.7 (2CO). MS (MALDI, positive mode, matrix DHB) $m/z$: 408.49 $(M + Na)^+$. Anal. Calcd for $C_{24}H_{23}N_3O_2$ (385.47): C, 74.78; H, 6.01; N, 10.90. Found: C, 74.82; H, 6.07; N, 10.96.

## BIOLOGY

**Cytotoxicity of the Synthesized Compounds Using the MTT assay.** MCF-7 cancer cells were cultured in complete media of DMEM at 5% carbon dioxide and 37 °C following the standard tissue culture work. The cells were grown in "10% fetal bovine serum and 1% penicillin−streptomycin" in the 96-multiwell plate. The synthesized compounds **9c**, **9d**, **9e**, and **9g** were screened for their cytotoxicity using the MTT assay (Promega, USA) for 48 h[34] using untreated and treated cells with concentrations of "0.01, 0.1, 1, 10, and 100 $\mu$M" for 48 h.

**EGFR Inhibition.** Compounds were subjected to EGFR kinase assay kit catalog #40321 using ELISA kit (enzyme-linked immunosorbent assay) following manufacturer information.[35] A microplate reader equipped with an ELISA reader (PerkinElmer) was used to measure the luminescence at 450 nm. Evaluation of inhibition percentage was calculated using this equation: $100 - \left[\frac{A_{control}}{A_{treated}} - \text{control})\right]$, $IC_{50}$ calculation was determined using GraphPad prism7.

**Molecular Docking Study.** Protein and chemical structures were optimized and generated by using Maestro. Next, the grid-box dimensions around the cocrystallized ligands were used to identify the binding site inside the proteins. The AutoDock Vina program was used to dock the compounds under investigation against the EGFR protein structures (PDB = 1M17) following routine work.[36]

## CONCLUSIONS

A series of 2-quinolone derivatives were prepared via chemoselective reactions of heterocyclic amides with acrylic acid derivatives. *N*-Alkyl-3-[2-oxoquinolin-1(2*H*)-yl]-propanamides were synthesized and characterized by using NMR spectroscopic analyses. Among derivatives, compound **9e** exhibited potent cytotoxicity against MCF-7 cells with an $IC_{50}$ value of 1.32 $\mu$M compared to doxorubicin ($IC_{50}$ = 1.21 $\mu$M). Additionally, it caused potent EGFR inhibition by 97% with an $IC_{50}$ value of 16.89 nM compared to that of Erlotinib. Finally, a molecular docking study was performed to highlight the virtual mechanism of binding toward EGFR. Hence, compound **9e** may be further developed as a promising target-oriented chemotherapeutics through future in vivo animal models.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c03114.

Spectroscopic characterizations of the synthesized compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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