SYNTHESIS, ABTS-RADICAL SCAVENGING ACTIVITY, AND ANTIProLIFERATIVE AND MOLECULAR DOCKING STUDIES OF NOVEL PYRROLO[1,2-a] QUINOLINE DERIVATIVES

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GRAPHICAL ABSTRACT

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Abstract A new 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS)-radical scavenging and antiproliferative agents of pyrrolo[1,2-a]quinoline derivatives have been synthesized. An efficient method for the synthesis of 14 novel diversified pyrrolo[1,2-a]quinoline derivatives has been described using 4-(1,3-dioxolan-2-yl)quinoline and different phenacyl bromides in acetone and followed by reacting with different acetylenes in dimethylformamide/K₂CO₃. The structure of the newly synthesized compounds was determined by infrared, ¹H NMR, ¹³C NMR, mass spectrometry, and elemental analysis. The in vitro antioxidant activity revealed that among all the tested compounds 5n exhibited maximum scavenging activity with ABTS. Compound 5b has showed good antiproliferative activity as an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase.

Keywords ABTS-radical scavenging activity; antiproliferative activity; 1,3-dipolar cycloaddition; molecular docking; pyrrolo[1,2-a]quinoline; quinoline 4-carbaldehyde

INTRODUCTION

Reactive oxygen species (ROS) play a critical role in cardiovascular diseases, inflammatory diseases, neurodegenerative disorders, cancer, and aging.¹ Antioxidants are compounds that detoxify ROS and prevent their damage through multimechanisms.² Cancer is one of the highest impact disease worldwide with significant morbidity and mortality rates. A key regulator of tissue homeostasis is the apoptosis or programmed cell death and the imbalances between cell death and proliferation, which may result in tumor formation.³ The objective of using anticancer agents is to induce apoptosis-related signaling in cancer cells while disrupting their proliferation.⁴ The time has come where synthesis of a newer class of anticancer agents is very much needed.

The chemistry of N-bridged heterocyclic compounds such as indolizines,⁵ azaindolizines,⁶ and benzoindolizines⁷ has important biological and physical applications. Among these, the pyrrolo[1,2-a]quinoline derivatives are significant because of their potential biological activities including antitumor,⁸ gastric (H+/K+)-ATPase inhibitor,⁹ antineoplastic,¹⁰ anti-inflammatory,¹¹ anti-malarial,¹² antiasthmatic,¹³ antidiabetic,¹⁴ antibacterial,¹⁵ in vitro antifungal,¹⁶ immunosuppressive,¹⁷ HIV-1 integrase inhibitory,¹⁸ anti-breast-cancer,¹⁹ and antiproliferative activities.²⁰ Additionally, Tokuyama et al. have reported the

Figure 1. A few examples of pyrrolo[1,2-a]quinoline-containing natural products and pharmaceuticals.
isolation, total synthesis, and various biological studies of a natural alkaloid called gephyrotoxin enclosing pyrrolo[1,2-a]quinoline skeleton\(^{[21]}\) (Fig. 1). Because 1,3-dipolar cycloadditions were widely used for the versatile synthesis of highly functionalized \(N\)-bridged heterocyclic compounds including pyrroloquinolines from readily available substrates\(^{[22]}\) and, after going through several such descriptions related to significant biological activities of pyrrolo[1,2-a]quinolines, in this we report the 1,3-dipolar-assisted synthesis, antioxidant and antiproliferative activity, and docking study of various novel pyrrolo[1,2-a]quinoline derivatives.

In view of the biological importance of these compounds, it was planned to synthesize a new series of its derivatives and further evaluate them for in vitro antioxidant and antiproliferative activity against cervical carcinoma cell line HeLa using MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyltetrazolium bromide) assay. In addition, the in silico analysis was carried out with the synthesized derivatives to understand the mode of interaction with superoxide dismutase (SOD) and epidermal growth factor receptor (EGFR) tyrosine kinase using docking protocols.

RESULTS AND DISCUSSION

Chemistry

Synthesis of the targeted derivatives (5a–n) was carried out as depicted in Schemes 1 and 2. Usually, the synthesis of pyrrolo[1,2-a]quinolines by 1,3-dipolar cycloaddition of the quinolinium \(N\)-ylides implies the preparation and separation of quinolinium salts which in the second step by reaction with a suitable base afford the corresponding quinolinium \(N\)-ylides. In the presence of the suitable base and alkynes, the pyrrolo[1,2-a]quinolines are obtained by 1,3-dipolar cycloaddition reaction. The first step of the reaction is the quaternization and isolation of 4-(1,3-dioxolan-2-yl)quinoline (2) with 2-bromoacetophenone (3) into quinolinum bromide (4). Subsequently, quinolinium bromide (4) was treated with different symmetrical alkynes (ethylpropiolate, dimethyl acetylenedicarboxylate, and diethyl acetylenedicarboxylate) in the presence of activated \(K_2CO_3\) as base in dimethylformamide (DMF). In this protocol, first the deprotonation of quinolinium bromides (4a–e) occurs by the action of the base. Subsequently, the 1,3-dipolar cycloaddition between an intermediate \(N\)-ylide (7a–n) and symmetrical alkynes (ethyl propiolate, dimethyl

![Scheme 1. Synthesis of pyrrolo[1,2-a]quinoline derivatives (5a–n).](image)
acetylenedicarboxylate, and diethyl acetylenedicarboxylate) has led to construction of pyrrolo[1,2-α]quinolines (5α–n).\textsuperscript{[23]}

Our aim in this work was to develop a simple and mild procedure for the synthesis of pyrrolo[1,2-α]quinoline derivatives from substituted quinoline. The materials for the synthesis of pyrrolo[1,2-α]quinolines (5α–n) were 4-formyl quinoline (1), substituted 2-bromoacenaphthalones (3α–e), and substituted alkynes.

The structures of the new compounds (5α–n) were assigned on the basis of $^1$H NMR, $^{13}$C NMR, mass spectra, and elemental analysis. $^1$H NMR spectrum of 5α showed a triplet at $\delta$ 1.31 (3H) and a quartet at $\delta$ 4.30 (2H) ppm corresponding to an ethyl ester group at position C-2 and the multiplet at $\delta$ 4.13 (4H) ppm corresponding to the presence of a dioxalan ring. $^{13}$C NMR spectrum of 5α has showed peaks at $\delta$ 162.9 (COO-CH$_2$-CH$_3$), 59.9 (O-CH$_2$), 14.21 (CH$_3$), 64.95 (O-CH$_2$), and 184.3 (CO-Ar) ppm, corresponding to ethyl ester, dioxalan ring, and carbonyl group in the COAr respectively. Infrared (IR) spectrum of 5α revealed that the appearance of the characteristic band at 1632 and 1748 cm$^{-1}$ corresponds to carbonyl group in the COAr and for ethyl ester C=O stretch respectively. Additionally, the liquid chromatography–mass spectrometry (LC-MS) has supported through a peak at 415 corresponding to the molecular weight of the compound 5α. Finally, the elemental analysis also supported the compound 5α. Similarly, the remaining compounds (5β–n), shown in Tables 1 and 2, were confirmed. These compounds were then tested for antioxidant, antiproliferative, and molecular docking studies.

### In Vitro Antioxidant Activity

**ABTS** [2,2′-Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)] radical cation scavenging method\textsuperscript{[24]}. The preformed radical monocation of 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) is generated by oxidation of ABTS.

| Entry | Compound | Ar | Yield (%) |
|-------|----------|----|-----------|
| 1     | 4a       | H  | 96        |
| 2     | 4b       | 4-Cl| 94        |
| 3     | 4c       | 4-Br| 93        |
| 4     | 4d       | 4-F | 94        |
| 5     | 4e       | 4-CH$_3$| 92       |
with potassium persulfate (a blue chromogen) and is reduced in the presence of such hydrogen donating antioxidants.

Solution I: ABTS (2 mM solution is prepared using distilled water).
Solution II: Potassium persulfate (17 mM solution is prepared using distilled water).

An aliquot of 0.3 mL of solution II was added to 50 mL of solution. The reaction mixture was left to stand at room temperature overnight in the dark before use.

Then, 1 mg of each of the drug samples was accurately weighed and dissolved in 1 mL of dimethylsulfoxide (DMSO). One mL of distilled DMSO was added to 0.2 mL of the drug samples or standard, and 0.16 mL of ABTS solution was added to make a final volume of 1.36 mL. Absorbance was measured spectrophotometrically after 7 min at 734 nm. A blank was maintained without ABTS. The radical scavenging activity (\%) is calculated by the following formula:

\[
\text{ABTS radical scavenging capacity} = \left( \frac{\text{Absorbance of control} - \text{Absorbance of sample}}{\text{Absorbance of control}} \right) \times 100
\]

ABTS radical scavenging capacity assay is an electron-transfer-based assay, which measures the capacity of an antioxidant to reduce an oxidant, which changes color when reduced. The degree of color change is correlated with the sample's antioxidant concentration.

The ABTS assay, which is applicable for both lipophilic and hydrophilic antioxidants, showed various radical scavenging activities between the derivatives. According to Table 3 values ranged from 27.14 to 92.88\%, and compound 5n possessed the greatest ABTS radical scavenging activity (92.88\%) followed by the 5i and 5l derivatives (89.02\% and 87.44\%) respectively, derivatives 5e, 5m, 5h, 5b, 5d, 5j, 5g, 5c, 5f, 5a (85.72, 81.43, 75.71, 72.10, 68.57, 65.77, 57.86, 48.54, 35.78, 32.86\%), while the 5k derivative showed the lowest antioxidant capacity (27.14\%) after 7 min.
Antiproliferative Activity

Cell culture. A HeLa cell line was maintained in Dulbecco’s modified Eagle’s medium (DMEM) medium (GIBCO) supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS) and 1% antibiotic solution (penicillin 100 U/ml and streptomycin 100 µg/ml) at 37 °C in a humidified atmosphere of 95% air/5% CO₂. The medium was changed every second day, and cells were subcultured when confluency reached 95% by 0.25% trypsin containing 0.02% ethylene-diaminetetraacetic acid (EDTA) in phosphate-buffered saline (PBS) for 3 min at 37 °C.

MTT assay. The MTT assay was carried out as described previously to measure cell viability.[25] Ten thousand cells in 100 µL of DMEM media were seeded in the wells of a 96-well plate. After 24 h, existing media was removed and 100 µL of various concentrations of complexes was added and incubated for 48 h at 37 °C in a CO₂ incubator. Control cells were supplemented with 0.05% DMSO vehicle. At 48 h of incubation, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, supplied from Sigma, 10 µL of 5 mg/mL) was added to the plate. The contents of the plate were pipetted out carefully, the formazan crystals formed were dissolved in 100 µL of DMSO, and the absorbance was measured at 550 nm in a micro plate reader (Tecan, infinite F200 Pro). Experiments were performed in triplicate, and the results were expressed as mean of percentage inhibition. A graph of the concentration versus percentage growth inhibition was plotted, and the concentration at which 50% cell death occurred was considered as the IC₅₀ value. Before adding MTT, bright field images (Olympus 1X81, cell Sens Dimension software) were taken for visualizing the cell death.

The values obtained demonstrated that all the compounds presented cytotoxic effects in a dose-dependent manner. The set of compounds showed excellent inhibitory activity, the results of which are shown in Fig. 2. Microscopy images representing the cell death caused by the compounds are as seen in Fig. 3. HeLa cells have been reported to contain human papilloma virus 18 (HPV-18) sequences, a low expression of p53, and normal expression of pRB (retinoblastoma suppressor).[26]

| No. | Compound | Antioxidant activity (%) |
|-----|----------|--------------------------|
| 1   | 5a       | 32.86                    |
| 2   | 5b       | 72.10                    |
| 3   | 5c       | 48.54                    |
| 4   | 5d       | 68.57                    |
| 5   | 5e       | 85.72                    |
| 6   | 5f       | 35.78                    |
| 7   | 5g       | 57.86                    |
| 8   | 5h       | 75.71                    |
| 9   | 5i       | 89.02                    |
| 10  | 5j       | 65.77                    |
| 11  | 5k       | 27.14                    |
| 12  | 5l       | 87.44                    |
| 13  | 5m       | 81.43                    |
| 14  | 5n       | 92.88                    |
Figure 2. Percentage inhibition of cell growth at different concentrations of compounds 5a, 5b, 5c, 5d, 5e, 5h, 5i, 5l, 5n. Data are mean ± SE (n = 3).
But the epidermal growth factor receptor is the first identified member of the type I receptor tyrosine kinase family and is a major regulator of several distinct, diverse cellular pathways. Selective compounds have been developed that target either the extracellular ligand-binding region of the EGFR or the intracellular tyrosine kinase region. This results in interference with the signalling pathways that modulate mitogenic and other cancer-promoting responses such as cell motility, cell adhesion, invasion, and angiogenesis.\textsuperscript{[27]} It is important to correlate the structure of these compounds with their biological effect, which will be valuable to propose new lead compounds with better cytotoxic potential.

**Molecular Docking Studies**

The three-dimensional structure of target protein superoxide dismutase (SOD) and EGFR tyrosine kinase having keyword 1CB4 and 2J5 F was downloaded from the PDB (\url{www.rcsb.org/pdb}) structural database. This file was then opened in SPDB viewer and edited by removing the heteroatoms and adding C terminal oxygen. The active pockets on target protein molecule were found out using the CASTp server.\textsuperscript{[28]} The ligands were drawn using ChemDraw Ultra 6.0 and assigned with proper two-dimensional (2D) orientation (ChemOffice package). Three-dimensional (3D) coordinates were prepared using a PRODRG server.\textsuperscript{[29]} Autodock V3.0 was used to perform automated molecular docking in AMD Athlon 2 × 2 215 at 2.70 GHz, with 1.75 GB of RAM. AutoDock 3.0 was compiled and run under Microsoft Windows XP service pack 3. For docking, a grid map is required in AutoDock, and the size of the grid box was set at 82, 82, and 100 Å (R, G, and B) and grid center 16.191, 70.024, and 15.326 for x, y, and z coordinates for SOD. However, 102, 126, and 118 Å (R, G, and B) and grid center −58.865, −8.115, and −24.556 were used for x, y, and z coordinates for EGFR tyrosine kinase. All torsions were allowed to rotate during docking. The Lamarckian genetic algorithm and the pseudo-Solis and Wets methods were applied for minimization, using default parameters.\textsuperscript{[30]} The newly synthesized compounds were taken as ligands and docked against target molecules.

To identify potential antioxidant lead among compounds 5a–n, docking calculations were performed using Autodock v3. After docking the synthesized molecule with superoxide dismutase, the compounds were bound exactly at the active site of superoxide dismutase, which is shown in Fig. 4. A careful inspection of the binding
pocket indicated that the active site of SOD was similar in all synthesized compounds at the Cu-Zn domain of SOD (Fig. 5). Target information and docking details for the compounds are tabulated in Table 4, which may provide useful information for in-depth understanding of binding mechanism of the compound to the active site of the protein. Hydrogen bond formation also makes important contributions to the interaction between ligand and the receptor. All 14 molecules showed good binding energy and docking energy ranging from $-6.27 \text{ kJ mol}^{-1}$ to $-10.28 \text{ kJ mol}^{-1}$ and $-8.87 \text{ kJ mol}^{-1}$ to $-13.61 \text{ kJ mol}^{-1}$ respectively. Among the 14 molecules, docking of SOD with compound 5i followed by compound 5n revealed three hydrogen bonds and their binding energies and docking energies were $-10.28$, $-9.88 \text{ kJ mol}^{-1}$ and $-13.61$, $-11.18 \text{ kJ mol}^{-1}$ respectively, and these two compounds may be considered as the lead molecules to increase the activity of superoxide dismutase and reduce

Figure 4. Interaction of synthesized molecules with superoxide dismutase.
oxidative stress. In in vitro studies compound 5n has also emerged as an active molecule. Hence, from the study it has been proved that molecule 5n is one of the potent antioxidant molecules.

Figure 4. Continued.
Based on the antiproliferative activity results, it was worthwhile to perform docking studies for supportive coordination between in silico studies with the in vitro results. The 14 derivatives docked with EGFR tyrosine kinase domain revealed that our synthesized derivatives are having inhibitory potential and exhibiting interactions with one or the other amino acids in the active pockets.

Figure 5. Ligplot results for SOD. (a) Binding of ligand CU on A-chain amino acids present in an active pocket of SOD with two hydrogen bonds. (b) Binding of ligand CU on A-chain amino acids present in another active pocket of SOD with six hydrogen bonds. (c) Binding of ligand ZN on B-chain amino acids present in an active pocket of SOD with six hydrogen bonds.

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as shown in Fig. 6. The docking results of synthesized derivatives are documented in Table 5. Derivatives 5b, 5h, and 5n showed $-6.16$, $-5.93$, and $-6.11 \text{kJ mol}^{-1}$ binding energy with three hydrogen bonds respectively, whereas derivative 5l showed $-5.61 \text{kJ mol}^{-1}$ binding energy with two hydrogen bonds with the target receptor, which indicates that among the nine derivatives 5l is the less efficient derivative. From the study it is evident that derivative 5b is a more efficient molecule for antiproliferative activity and a good inhibitor of EGFR tyrosine kinase.

| Molecule | Binding energy | Docking energy | Inhibitory constant | Intermol energy | H bonds | Bonding |
|----------|----------------|----------------|---------------------|----------------|---------|---------|
| 5a       | $-6.67$        | $-8.87$        | $1.29e-005$         | $-8.54$        | 3       | $5a::DRG1:OAZ:SOD:A:ALA1:HN2$
| 5b       | $-8.31$        | $-10.29$       | $8.17-007$          | $-10.48$       | 3       | $5b::DRG1:OBG:SOD:A:VAL7:O$
| 5c       | $-7.87$        | $-11.33$       | $1.71e-006$         | $-10.67$       | 3       | $5c::DRG1:OBC:SOD:B:THR56:HN$
| 5d       | $-8.83$        | $-10.55$       | $3.35e-007$         | $-10.7$        | 2       | $5d::DRG1:OAR:SOD:B:LYS9:O$
| 5e       | $-9.01$        | $-11.46$       | $2.47e-007$         | $-11.19$       | 3       | $5e::DRG1:OOA:SOD:A:ASN51:HD22$
| 5f       | $-7.58$        | $-10.76$       | $2.77e-006$         | $-10.38$       | 3       | $5f::DRG1:OBC:SOD:B:ASP11:HN$
| 5g       | $-8.47$        | $-10.04$       | $6.16e-007$         | $-10.34$       | 2       | $5g::DRG1:OCA:SOD:A:ASN51:HD22$
| 5h       | $-8.99$        | $-11.11$       | $2.57e-007$         | $-11.17$       | 3       | $5h::DRG1:OAR:SOD:B:ASN51:O$
| 5i       | $-10.28$       | $-13.61$       | $2.91e-008$         | $-13.08$       | 3       | $5i::DRG1:OAR:SOD:B:LYS9:O$
| 5j       | $-8.28$        | $-9.63$        | $8.57e-007$         | $-10.14$       | 3       | $5j::DRG1:OAO:SOD:A:ASN51:HD22$
| 5k       | $-6.27$        | $-9.02$        | $2.54e-005$         | $-8.45$        | 3       | $5k::DRG1:OAZ:SOD:A:SER109:HG$
| 5l       | $-9.65$        | $-13.23$       | $8.42e-008$         | $-12.45$       | 3       | $5l::DRG1:OBG:SOD:B:GLY54:HN$
| 5m       | $-9.02$        | $-11.18$       | $2.44e-007$         | $-10.89$       | 2       | $5m::DRG1:OAR:SOD:B:LYS9:O$
| 5n       | $-9.88$        | $-11.18$       | $5.72e-008$         | $-12.06$       | 3       | $5n::DRG1:OBG:SOD:B:GLY54:HN$

Table 4. Molecular docking results with superoxide dismutase
EXPERIMENTAL

Chemicals were purchased from SD-fine and Sigma-Aldrich companies and were used without further purification. All products were characterized by comparison of their IR, $^1$H NMR, and $^{13}$C NMR spectra. All yields refer to the isolated products. The purity determinations of the substrates, products, and reaction monitoring were accomplished by thin-layer chromatography (TLC) on silica-gel polygram SIL/UV 254 plates. IR spectra were recorded on an infrared Fourier transform spectrometer. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) were recorded on a Bruker Avance 400 instrument using tetramethylsilane (TMS) as an internal standard and CDCl$_3$ or dimethylsulfoxide (DMSO-d$_6$) as solvent. Melting points were recorded in open capillary tubes. LC-MS analysis was performed on Agilent LC-1200 series coupled with 6140 single quad mass spectrometer with electron ionization (ESI) +ve and –ve mode, MS range 100–2000. Elemental analyses were recorded using Perkin Elmer CHNS analyzer.

### Table 5. Docking results of synthesized molecules with EGFR tyrosine kinase

| Molecule | Binding energy | Docking energy | Inhibitory constant | Intermol energy | H bonds | Bonding |
|----------|----------------|----------------|---------------------|-----------------|---------|---------|
| 5a       | –6.55          | –8.67          | 1.59e-005           | –9.35           | 2       | 5a::DRG:O:TK:A:LEU703:HN         |
| 5a       | –6.16          | –8.72          | 3.05e-005           | –8.34           | 3       | 5b::DRG:OAZ:TK:A:ASP837:OD2 |
| 5b       | –7.47          | –9.76          | 3.33e-006           | –9.65           | 2       | 5c::DRG:OBC:TK:A:ARG841:HE |
| 5c       | –7.66          | –9.51          | 2.41e-006           | –9.53           | 2       | 5d::DRG:OAO:TK:A:LYS879:HZ3 |
| 5d       | –5.96          | –8.86          | 4.31e-005           | –8.76           | 2       | 5e::DRG:OAQ:TK:A:LEU703:HN |
| 5e       | –5.93          | –8.57          | 4.48e-005           | –8.11           | 3       | 5f::DRG:OAR:TK:A:ASP770:OD2 |
| 5f       | –5.89          | –8.73          | 4.82e-005           | –8.69           | 2       | 5g::DRG:OAR:TK:A:ASP770:OD1 |
| 5g       | –5.61          | –9.29          | 7.72e-005           | –8.41           | 2       | 5h::DRG:OBH:TK:A:ARG776:HH12 |
| 5h       | –6.11          | –8.55          | 3.32e-005           | –8.29           | 3       | 5i::DRG:OBH:TK:A:ARG836:HH11 |
| 5l       | –5.93          | –8.57          | 4.48e-005           | –8.11           | 3       | 5j::DRG:OBH:TK:A:ARG841:HE |
| 5n       | –6.11          | –8.55          | 3.32e-005           | –8.29           | 3       | 5k::DRG:OBH:TK:A:ARG836:HH12 |

**Synthesis of Ethyl 1-(4-Chlorobenzoyl)-5-(1,3-dioxolan-2-yl)pyrrolo[1,2-a]quinoline-2-carboxylate (5d)**

To a stirred solution of 1-[2-(4-chlorophenyl)-2-oxoethyl]-4-(1,3-dioxolan-2-yl) quinoliniumbromide (4b) (100 mg, 0.230 mmol) in dry DMF, ethyl propiolate (0.03 mL, 0.230 mmol) and K$_2$CO$_3$ were added. Stirring was continued for 2 h at room temperature. Completion of reaction was monitored by TLC. The reaction mass was quenched by ice-cold water. Solids were separated out, filtered, and dried.
under vacuum to afford 94 mg (0.204 mmol) of a pale yellow solid, titled compound 5d. Similarly, other compounds of the series 5a–n were prepared.

**Ethyl 1-(4-Chlorobenzoyl)-5-(1,3-dioxolan-2-yl)pyrrolo[1,2-a]quinoline-3-carboxylate (5d)**

Brownish yellow solid, mp 150–155 °C; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta =$ 1.31 (t, 3H), 4.16–4.17 (m, 4H), 4.36–4.38 (m, 2H), 6.44 (s, 1H), 7.50–7.52 (m, 5H), 8.01–8.02 (m, 3H), 8.19 (dd, $J =$ 1.20, 8.00 Hz, 1H), 8.60 (s, 1H) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta =$ 14.47, 60.28, 65.43, 101.00, 108.76, 115.17, 120.43, 123.04, 125.52, 125.67, 126.20, 127.98, 128.55, 128.86, 129.02, 129.42, 131.46, 133.14, 134.84, 136.68, 139.40, 139.49, 163.84, 183.57 ppm; $m/z$ 449 [M+H]$^+$. Anal. calcd. for C$_{25}$H$_{20}$ClNO$_5$: C, 66.74; H, 4.48; N, 3.11. Found: C, 66.76; H, 4.45; N, 3.09.

**Figure 6.** Enfolding of synthesized molecules in the active pocket of EGFR tyrosine kinase with hydrogen bonding.
Figure 6. Continued.
CONCLUSIONS

The research work was focused on developing a simple and mild procedure for the synthesis of pyrrolo[1,2-a]quinoline derivatives from substituted quinoline. The reactions performed are ecofriendly as they are carried out at room temperature. The structures have been confirmed by spectroscopic techniques such as $^1$H NMR, $^{13}$C NMR, and mass. Based on the results of in silico studies and the in vitro activity, derivative 5n showed radical scavenging activity and 5b has been proved to be one of the potent antiproliferative agents. Hence, 5n and 5b can be used as efficient antioxidant and antiproliferative products.

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SUPPLEMENTAL MATERIAL

Full experimental details, $^1$H and $^{13}$C NMR spectra, and LCMS spectra for this article can be accessed on the publisher’s website.

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