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Synthesis, ABTS-Radical Scavenging Activity, and Antiproliferative and Molecular Docking Studies of Novel Pyrrolo[1,2-*a*]quinoline Derivatives

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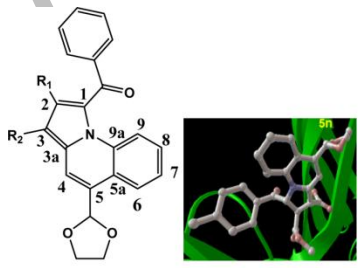
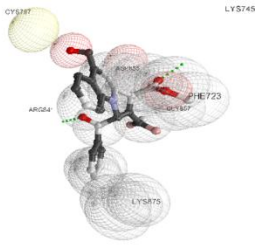
Abstract

A new ABTS-radical scavenging and antiproliferative agents of pyrrolo[1,2-*a*]quinoline derivatives have been synthesized. An efficient method for the synthesis of fourteen 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 DMF/K_2CO_3. The structure of the newly synthesized compounds was determined by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis. The *in vitro* antioxidant activity revealed that, among all the tested compounds **5n** has exhibited maximum scavenging activity with ABTS. The compound **5b** has showed good antiproliferative activity as good inhibitor of EGFR tyrosine kinase.



5a-n



5b

KEYWORDS: Pyrrolo[1,2-*a*]quinoline, quinoline 4-carbaldehyde, 1,3-dipolar cycloaddition, antiproliferative activity, ABTS-radical scavenging activity, molecular docking

1. 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 impacting 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]. To induce apoptosis-related signaling in cancer cells while disrupting their proliferation were the objective of using anticancer agents [4]. The time has come where synthesis of a newer class of anticancer agents is in very much need.

The chemistry of *N*-bridged heterocyclic compounds like indolizines [5], azaindolizines [6] and benzoindolizines [7] has certainty due to their important biological and physical applications. Among these, the pyrrolo[1,2-*a*]quinoline derivatives are significant due to their potential biological activities including antitumor [8], gastric (H+/K+)–ATPase inhibitor [9], antineoplastic [10] anti-inflammatory [11], antimalarial [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 isolation, total synthesis

and various biological studies of a natural alkaloid called gephyrotoxin enclosing pyrrolo[1,2-*a*]quinoline skeleton [21] (**Fig 1**). Since, 1,3-dipolar cycloadditions were widely used for the versatile synthesis of highly functionalized *N*-bridged heterocyclic compounds including pyrroloquinolines from the readily available substrates [22] and after going through above such several descriptions related to significant biological activities of pyrrolo[1,2-*a*]quinolines, we in this, reported 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 was further evaluated for its *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 in order to understand the mode of interaction with SOD (superoxide dismutase) and EGFR (epidermal growth factor receptor) tyrosine kinase using docking protocols.

2. RESULTS AND DISCUSSION

2.1. 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 presence of the suitable base and alkynes, the pyrrolo[1,2-*a*]quinolines are obtained by 1,3-dipolar cycloaddition reaction. 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, the 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 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 acetylenedicarboxylate and diethyl acetylenedicarboxylate) has led to construction of pyrrolo[1,2-*a*]quinolines (**5a-n**) [23].

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

The structures of the new compounds (**5a-n**) were assigned on the basis of ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. ^{1}H NMR spectrum of **5a** showed a triplet at δ 1.31 (3H) and a quartet at δ 4.30 (2H) ppm corresponds to an ethyl ester group at position C-2 and the multiplet at δ 4.13 (4H) ppm corresponds to the presence of dioxalan ring. ^{13}C NMR spectrum of **5a** has showed peaks at δ 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 corresponds to ethyl ester,

dioxalan ring and carbonyl group in the COAr respectively. IR spectrum of **5a** 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 LC-MS has supported through a peak at 415 corresponding to the molecular weight of the compound **5a**. Finally, the elemental analysis also supported for the compound **5a**. Similarly, the remaining compounds (**5b-n**), **Table 1 and 2** were confirmed. These compounds were then tested for antioxidant, antiproliferative and molecular docking studies.

2.2. In Vitro Antioxidant Activity

ABTS [2, 2'-Azinobis-(3-Ethylbenzothiazoline-6-Sulfonic Acid)] Radical Cation Scavenging Method: [24]

Principle

The pre-formed radical monocation of 2, 2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) is generated by oxidation of ABTS with potassium persulfate (a blue chromogen) and is reduced in the presence of such hydrogen donating antioxidants.

Chemicals and Reagents Used

Preparation of ABTS solution

Soution I: ABTS (2, 2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (2 mM solution isprepared using distilled water).

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

0.3 mL of solution II was added to 50 mL of solution. The reaction mixture was left to stand atroom temperature overnight in dark before use.

Preparation of Test Solution

1mg of each of the drug samples accurately weighedseparately and dissolved in 1 mL of DMSO.

Method

1 mL of distilled DMSO was added to 0.2 mL of the drug samples orstandard, 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. Blank was maintained without ABTS. The radical scavenging activity (%) is calculated by the following formula.

$$\frac{\text{Absorbance of control} - \text{Absorbance of sample}}{\text{Absorbance of control}} \times 100$$

ABTS radical scavenging capacity assay is an electron transfer based assaywhich measures the capacity of an antioxidant toreduce an oxidant, which changes color when reduced. Thedegree of color change is correlated with the sample's antioxidantconcentration.

ABTS assay which is applicable for both lipophilic and hydrophilic antioxidants, showed various radical scavenging activity between the derivatives. According to **Table 3** values ranged from 27.14 to 92.88 %, compound **5n** possessed the highest ABTS radical scavenging activity (92.88 %) followed by the **5i** and **5l** derivatives (89.02 % and 87.44 %) respectively, for derivative **5e, 5m, 5h, 5b, 5d, 5j, 5g, 5c, 5f** (85.72, 81.43, 75.71,

72.10, 68.57, 65.77, 57.86, 48.54, 35.78 %), and **5a** (32.86%), the **5k** derivative showed the lowest antioxidant capacity (27.14 %) after 7 minute.

2.3. Antiproliferative Activity:

Cell culture:

HeLa cell line was maintained in DMEM medium (GIBCO) supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS) and 1% antibiotic solution (penicillin 100Uml^{-1} and streptomycin 100µgml^{-1}) at 37°C in a humidified atmosphere of 95% air/5% CO_2. The medium was changed every second day, and cells were subcultured when confluency reach to 95% by 0.25% trypsin containing 0.02% ethylene-diaminetetraacetic acid (EDTA) in PBS for 3min at 37°C.

MTT Assay:

The MTT assay was carried out as described previously to measure cell viability [25]. Ten thousand cells in 100µL 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 CO_2 incubator. Control cells were supplemented with 0.05% DMSO vehicle. At the 48th hour of incubation, MTT (3-(4,5-dimethylthaizol-2-yl)-2,5-diphenyltetrazolium bromide- supplied from Sigma, 10µL 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 100µL 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]. 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 like cell motility, cell adhesion, invasion, angiogenesis etc [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.

2.4. Molecular Docking Studies

The three dimensional structure of target protein superoxide dismutase (SOD)and EGFR tyrosine kinase having keyword 1CB4 and 2J5F was downloaded from PDB

(www.rcsb.org/pdb) structural database. This file was then opened in SPDB viewer edited by removing the heteroatoms, adding C terminal oxygen. The active pockets on target protein molecule were found out using CASTp server [28]. The ligands were drawn using ChemDraw Ultra 6.0 and assigned with proper 2D orientation (ChemOffice package). 3D coordinates were prepared using PRODRG server [29] (Ghose and Crippen, 1987). Autodock V3.0 was used to perform Automated Molecular Docking in AMD Athlon (TM)2x2 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, grid map is required in AutoDock, 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, 15.326 for x, y, and z-coordinates for SOD while 102, 126 and 118 Å (R, G, and B), and grid center -58.865, -8.115, -24.556 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 [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 bound exactly at the active site of Superoxide dismutase, which was 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 were tabulated in **Table 4**, which may provide useful information for in- depth understanding in 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 the fourteen molecules showed good binding energy and docking energy ranging from -6.27 $kJmol^{-1}$ to -10.28 $kJmol^{-1}$ and -8.87 $kJmol^{-1}$ to -13.61 $kJmol^{-1}$ respectively. Among the fourteen molecules, docking of SOD with compound **5i** followed by compound **5n** revealed three hydrogen bonds and its binding energy and docking energy were -10.28, -9.88 $kJmol^{-1}$ and -13.61, -11.18, $kJmol^{-1}$ respectively, and these two compounds may be considered as the lead molecules to increase the activity of Superoxide dismutase and reduce oxidative stress. In *in vitro* studies also compound **5n** has emerged as an active molecule. Hence, from the study it has been proved that molecule **5n** to be one of the potent antioxidant molecules.

Based on the antiproliferative activity results, it was thought worthwhile to perform docking studies for supportive coordination between *in silico* studies with the *in vitro* results. The fourteen 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 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 $kJmol^{-1}$ binding energy with 3 hydrogen bonds respectively. Whereas derivative **5l** showed -5.61 $kJmol^{-1}$ binding energy with two hydrogen bonds with the target receptor, this indicates that among the nine derivatives **5l** is less efficient derivative. From the study it is evident that derivative **5b** is more efficient molecule for antiproliferative activity and good inhibitor of EGFR tyrosine kinase.

3. EXPERIMENTAL SECTION

Chemicals were purchased from SD-fine, Sigma-Aldrich companies and were used without further purification. All products were characterized by comparison of their IR, ^{1}HNMR and ^{13}CNMR spectra. All yields refer to the isolated products. The purity determination of the substrates, products and reaction monitoring were accomplished by 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 BrukerAvance 400 instrument using TMS as an internal standard and $CDCl_3$ or 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 ESI +ve and –ve mode, MS range 100-2000. Elemental analyses were recorded using Perkin Elmer CHNS analyzer.

Experimental Procedure For The 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)** (100mg, 0.230mmol) in dry DMF, ethyl propiolate (0.03mL, 0.230mmol) and K_2CO_3 were added. Stirring was continued for 2h 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 (94mg, 0.204mmol) of pale yellow solid of 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^{0}C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 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): δ = 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, 183.57ppm; 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.

4. CONCLUSIONS

The research work is focused on to develop a simple and mild procedure for the synthesis of pyrrolo[1,2-*a*]quinoline derivatives from substituted quinoline. The reactions performed are eco-friendly as they are carried out at room temperature. The structures have been confirmed by spectroscopic techniques like ^{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.

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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Table 1: Synthesis of quinolinium bromides (**4a-e**)

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

Table. 2. Pyrrolo[1,2-*a*]quinoline derivatives (**5a–n)**

Compound	**R_1**	**R_2**	**Yield (%)**	**M.p (^{0}C)**
5a	$COOC_2H_5$	H	92	142-146
5b	$COOCH_3$	$COOCH_3$	93	225-227
5c	$COOC_2H_5$	$COOC_2H_5$	90	160-162
5d	$COOC_2H_5$	H	91	150-155
5e	$COOCH_3$	$COOCH_3$	92	201-204
5f	$COOC_2H_5$	$COOC_2H_5$	93	218-220
5g	$COOC_2H_5$	H	89	140-145
5h	$COOCH_3$	$COOCH_3$	90	203-205
5i	$COOC_2H_5$	$COOC_2H_5$	91	152-155
5j	$COOC_2H_5$	H	90	155-158
5k	$COOCH_3$	$COOCH_3$	92	220-223
5l	$COOC_2H_5$	$COOC_2H_5$	91	165-169
5m	$COOC_2H_5$	H	91	148-151
5n	$COOCH_3$	$COOCH_3$	93	210-212

Table 3: % Antioxidant activity of compound **5a-n**

Sl. 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

Table 4: Molecular docking results with Superoxide dismutase

Molecules	**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 5a::DRG1:OAO:SOD:B:GLY106:HN 5a::DRG1:OBC:SOD:B:ILE111:O
5b	-8.31	-10.29	8.17-007	-10.48	3	5b::DRG1:OBG:SOD:A:VAL7:O 5b::DRG1:OBB:SOD:B:VAL146:HN 5b::DRG1:OAR:SOD:B:LYS9:O
5c	-7.87	-11.33	1.71e-006	-10.67	3	5c::DRG1:OBC:SOD:B:ASP11:HN 5c::DRG1:OAZ:SOD:B:THR56:HN 5c::DRG1:OAZ:SOD:B:THR56:HG1
5d	-8.83	-10.55	3.35e-007	-10.7	2	5d::DRG1:OAR:SOD:B:LYS9:O 5d::DRG1:OAZ:SOD:B:LYS9:HZ3
5e	-9.01	-11.46	2.47e-007	-11.19	3	5e::DRG1:OAO:SOD:A:ASN51:HD22

						5e::DRG1:OBG:SOD:A:VAL146:HN 5e::DRG1:OAO:SOD:A:LYS9:O
5f	-7.58	-10.76	2.77e-006	-10.38	3	5f::DRG1:OBD:SOD:B:CYS144:O 5f::DRG1:OAR:SOD:B:ASP11:HN 5f::DRG1:OAO:SOD:B:CYS55:HN
5g	-8.47	-10.04	6.16e-007	-10.34	2	5g::DRG1:OAR:SOD:A:ASN51:HD22 5g::DRG1:OBD:SOD:A:VAL146:HN
5h	-8.99	-11.11	2.57e-007	-11.17	3	5h::DRG1:OAR:SOD:B:ASN51:O 5h::DRG1:OBG:SOD:B:VAL146:HN 5h::DRG1:OBD:SOD:A:VAL146:HN
5i	-10.28	-13.61	2.91e-008	-13.08	3	5i::DRG1:OAR:SOD:B:LYS9:O 5i::DRG1:OBH:SOD:B:VAL146:HN 5i::DRG1:OBC:SOD:A:VAL146:HN
5j	-8.28	-9.63	8.57e-007	-10.14	3	5j::DRG1:OAO:SOD:A:VAL146:O 5j::DRG1:OAR:SOD:B:ASN51:HN

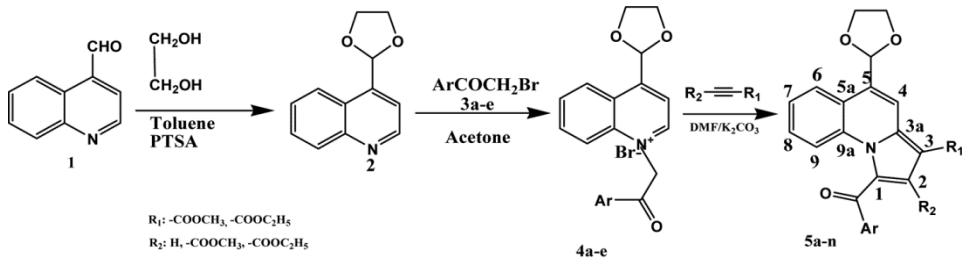
						5j::DRG1:OBD:SOD:B:ASN51:O
5k	-6.27	-9.02	2.54e-005	-8.45	3	5k::DRG1:OAZ:SOD:A:SER109:HG 5k::DRG1:OBG:SOD:B:ALA1:HN1 5k::DRG1:OBD:SOD:A:GLY106:O
5l	-9.65	-13.23	8.42e-008	-12.45	3	5l::DRG1:OBH:SOD:B:VAL146:HN 5l::DRG1:OAR:SOD:B:GLY54:HN 5l::DRG1:OAR:SOD:B:ASN51:O
5m	-9.02	-11.18	2.44e-007	-10.89	2	5m::DRG1:OAR:SOD:B:CYS144:O 5m::DRG1:OBD:SOD:A:VAL146:HN
5n	-9.88	-11.18	5.72e-008	-12.06	3	5n::DRG1:OBG:SOD:B:VAL146:HN 5n::DRG1:OBC:SOD:A:VAL146:HN 5n::DRG1:OAR:SOD:A:ASN51:HD22

Table 5: The 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::DRG:OBF:TK:A:ARG776:HE
5b	-6.16	-8.72	3.05e-005	-8.34	3	5b::DRG:OAZ:TK:A:ASP837:OD2 5b::DRG:OAY:TK:A:LYS745:HZ1 5b::DRG:O:TK:A:ARG841:HH11
5c	-7.47	-9.76	3.33e-006	-9.65	2	5c::DRG:OBC:TK:A:ASP855:OD2 5c::DRG:OBF:TK:A:MET793:HN
5d	-7.66	-9.51	2.41e-006	-9.53	2	5d::DRG:OBC:TK:A:ARG841:HE 5d::DRG:OAO:TK:A:LYS879:HZ3
5e	-5.96	-8.86	4.31e-005	-8.76	2	5e::DRG:OAQ:TK:A:LEU703:HN 5e::DRG:OBH:TK:A:ARG776:HH22
5h	-5.93	-8.57	4.48e-005	-8.11	3	5h::DRG:OAR:TK:A:ASP770:OD2

						5h::DRG:OBD:TK:A:ASP770:OD1 5h::DRG:OBC:TK:A:ARG776:HH12
5i	-5.89	-8.73	4.82e-005	-8.69	2	5i::DRG:OAR:TK:A:ASP770:O 5i::DRG:OAR:TK:A:ASN771:HD21
5l	-5.61	-9.29	7.72e-005	-8.41	2	5l::DRG:OBH:TK:A:ARG836:HH11 5l::DRG:OBH:TK:A:ARG836:HH21
5n	-6.11	-8.55	3.32e-005	-8.29	3	5n::DRG:OBC:TK:A:ARG803:HH21 5n::DRG:OBH:TK:A:ARG841:HE 5n::DRG:OAO:TK:A:LYS879:HZ3

Scheme 1: Synthesis of pyrrolo[1,2-a]quinoline derivatives **(5a-n)**



a: Ar=C_6H_5; b:Ar=4-FC_6H4; c: Ar=4-ClC_6H_4; d: Ar=4-BrC_6H_4; e: Ar=4-$CH_3C_6H_4$

Scheme 2: Proposed mechanism for synthesis of substituted pyrrolo[1,2-*a*]quinoline derivatives

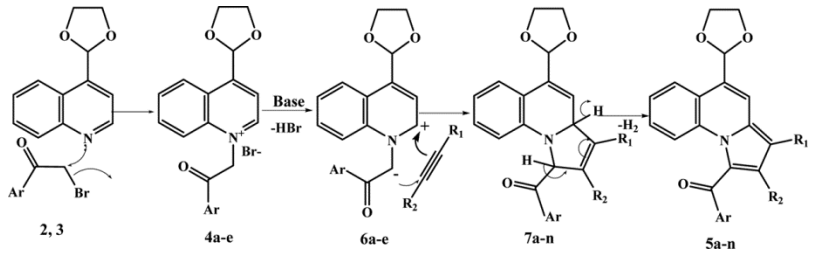


Figure 1. A few examples of pyrrolo[1,2-*a*]quinoline-containing natural products and pharmaceuticals

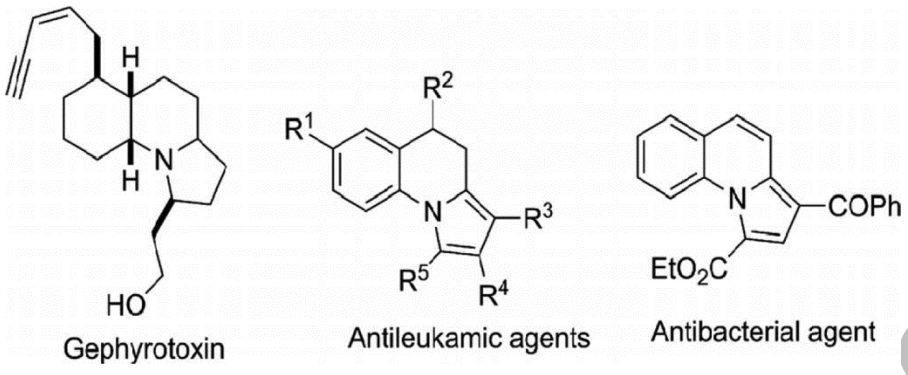


Figure 2. Percentage inhibition of cell growth at different concentrations of compounds **5a**; **5b**; **5c**; **5d**, **5e**, **5h**, **5i**, **5l**, **5n**. Data are Mean±SE (n=3).

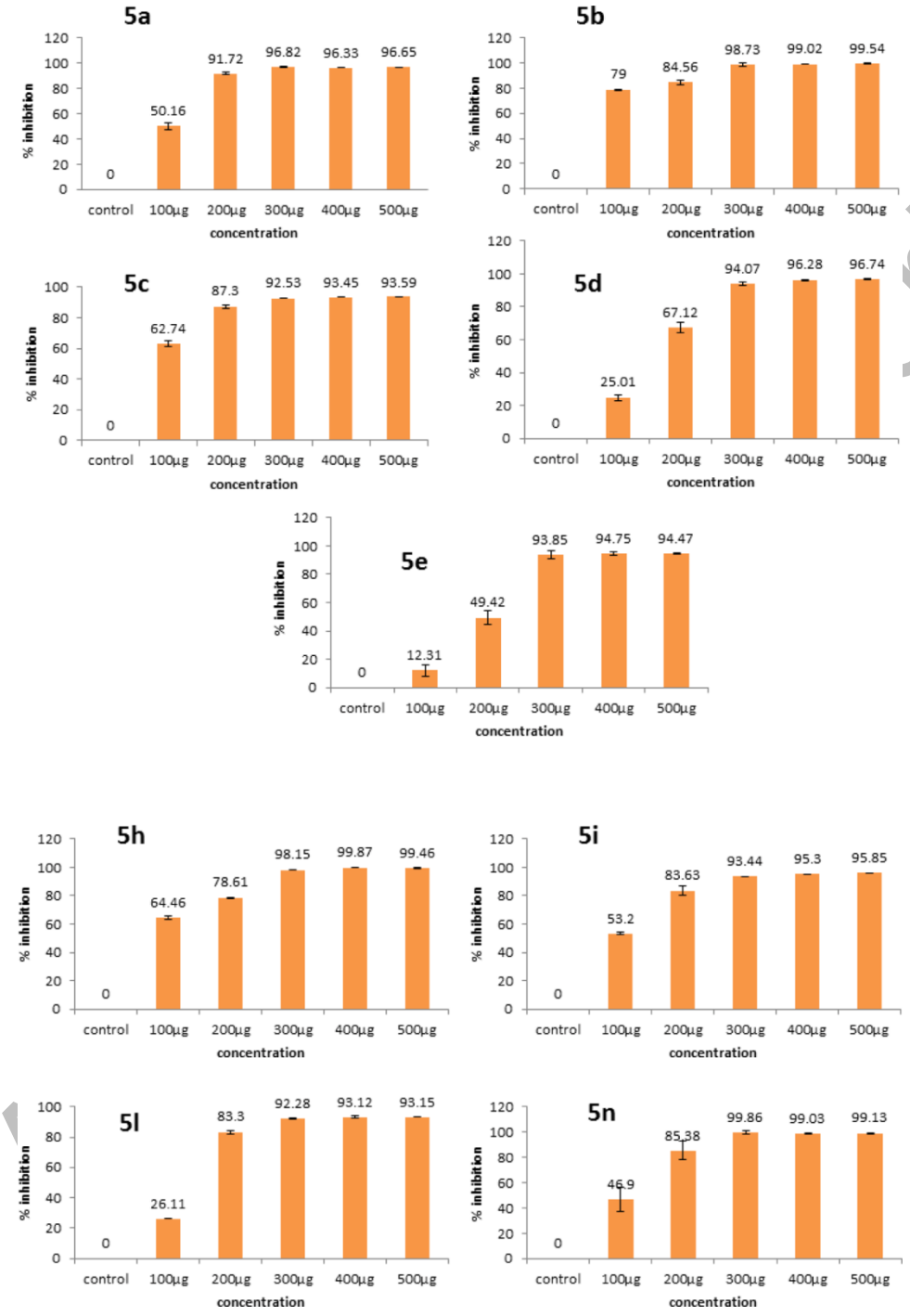


Figure 3: Anticancer activity of compounds showing cell death, A-control; B-treated**.**

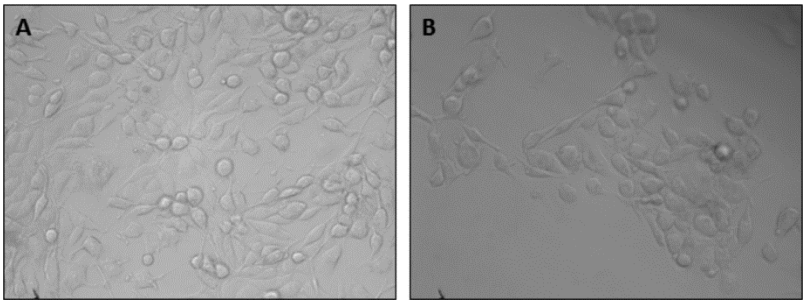
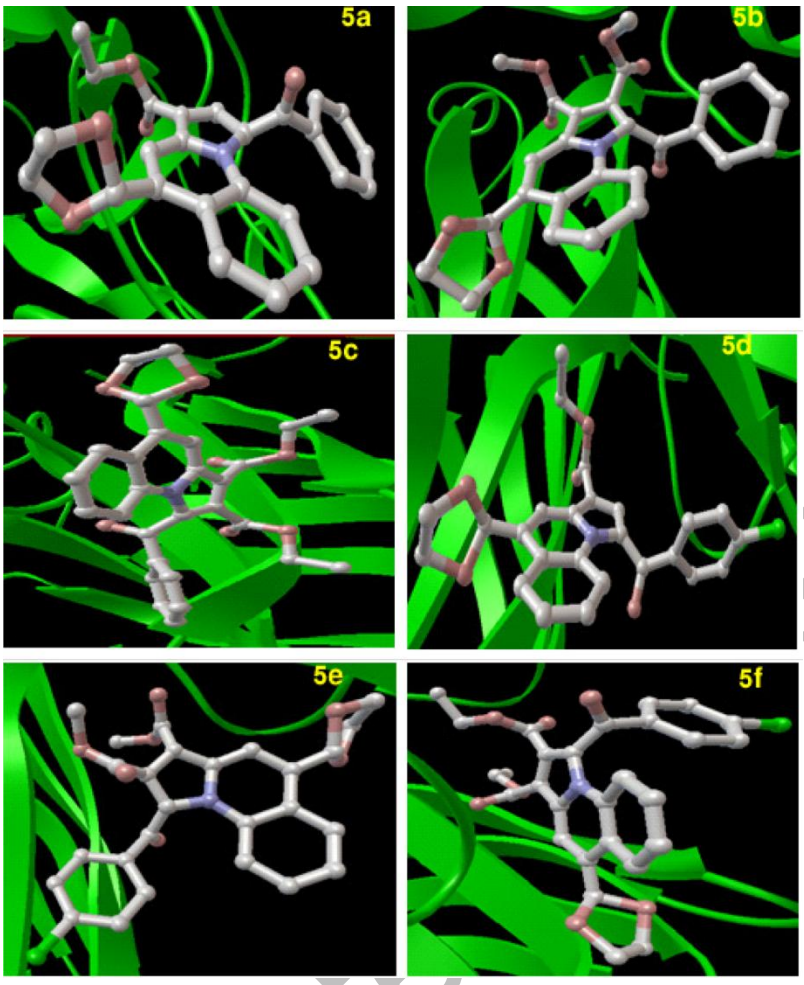


Figure 4: Interaction of synthesized molecules with superoxide dismutase.



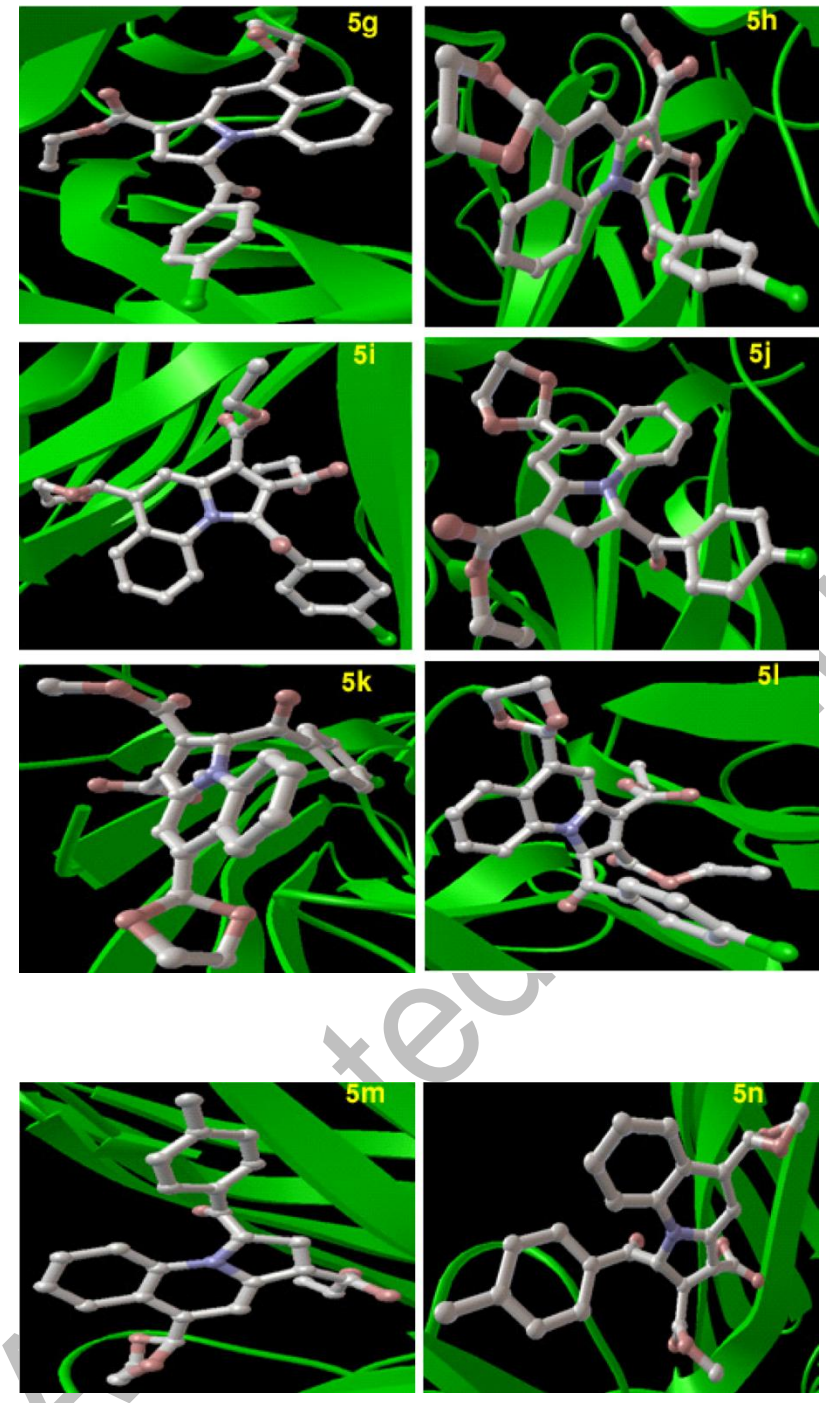


Figure 5: Ligplot results for SOD. **a**. Showing the binding of ligand CU on A-chain amino acids present in an active pocket of SOD with two hydrogen bonds. **b**. Binding of ligand CU on A-chain amino acids present in another active pocket of SOD with six hydrogen bonds. **c**. Showing the binding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

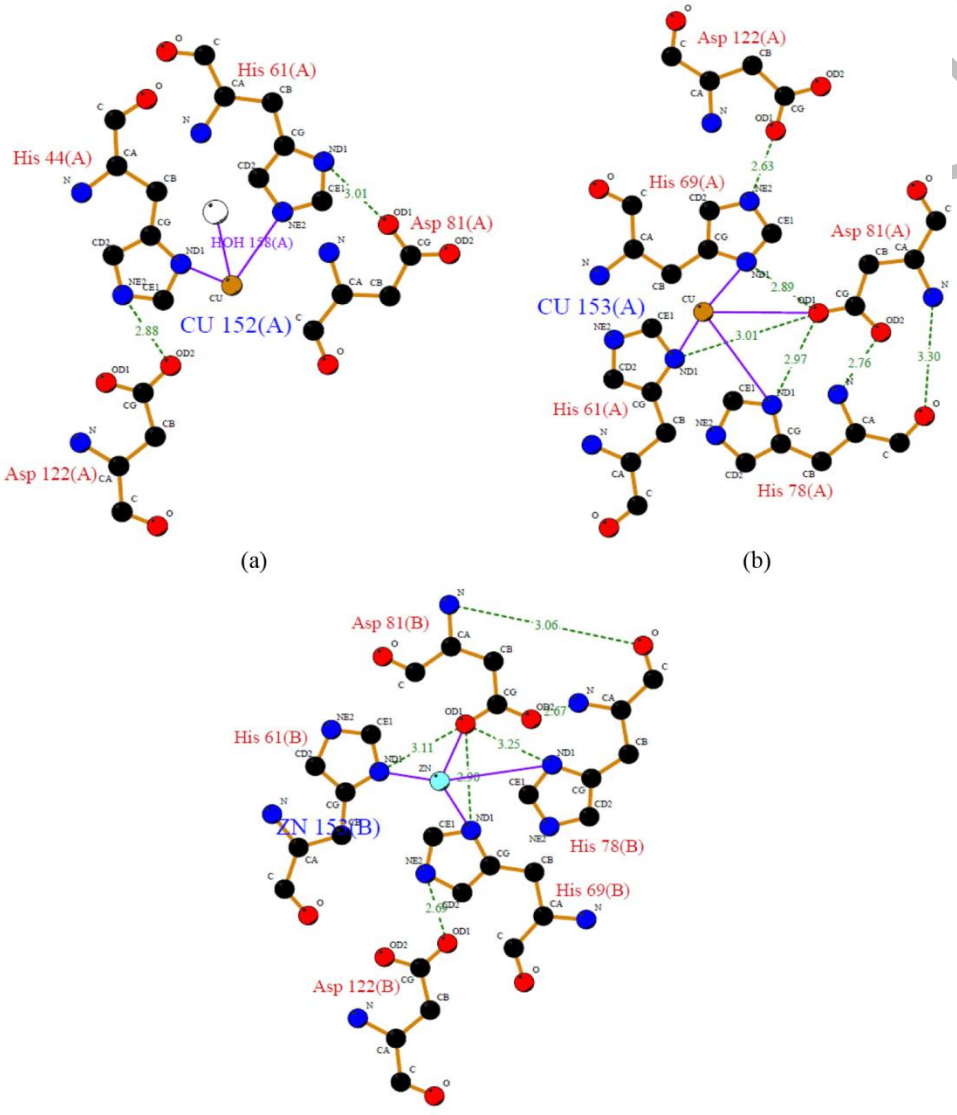
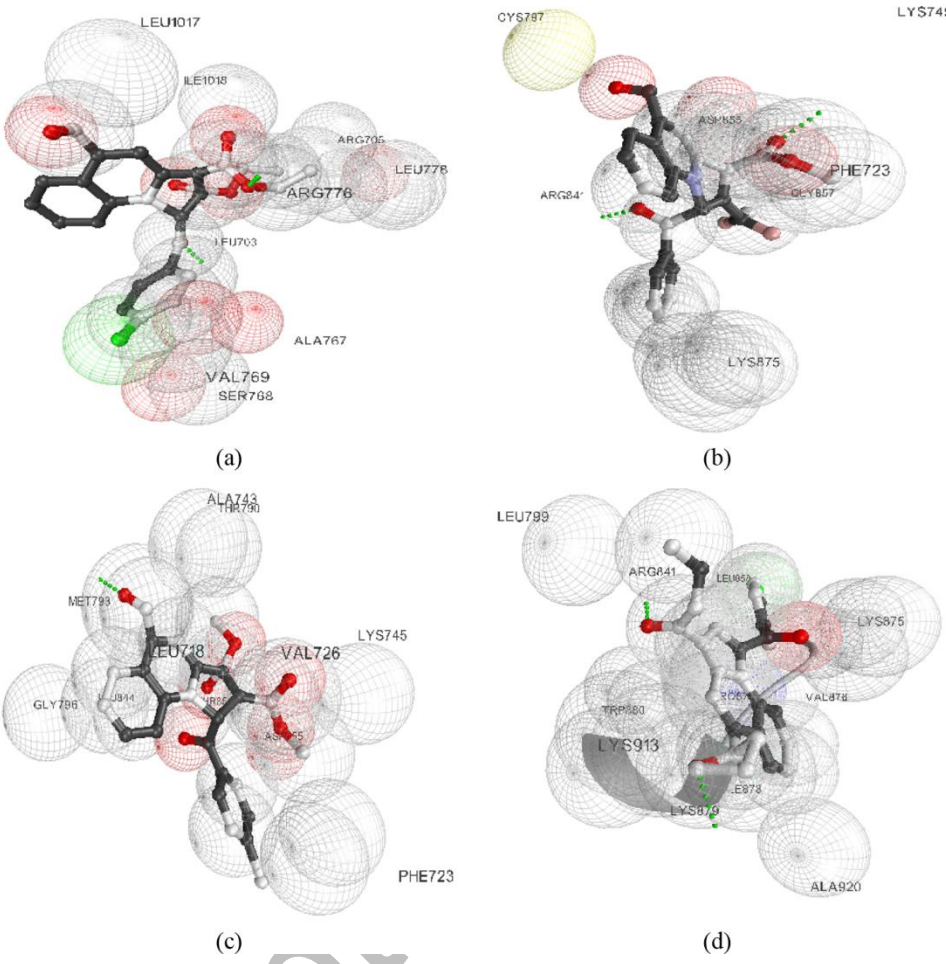
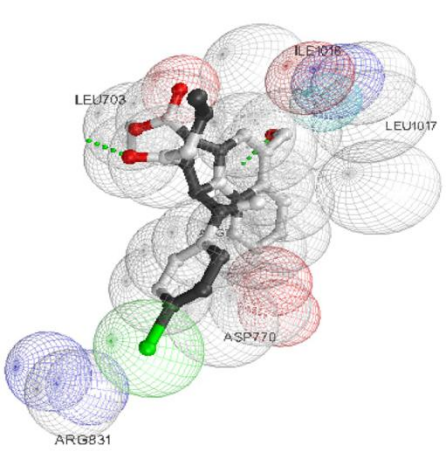
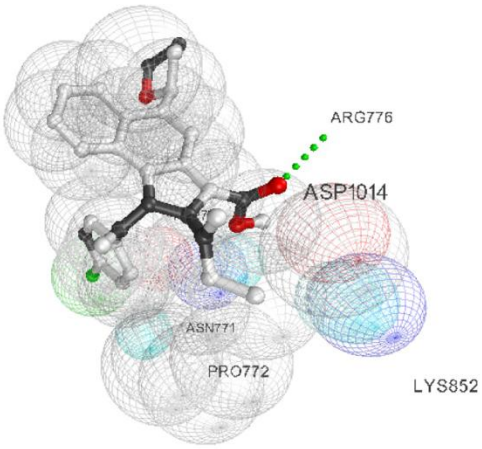


Figure 6: Enfolding of synthesized molecules in the active pocketof EGFR tyrosine kinase with hydrogen bonding.

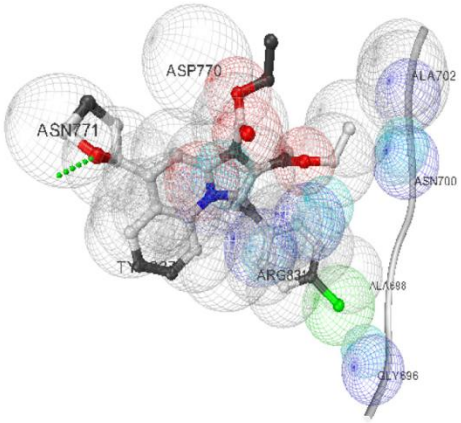




(e)



(h)



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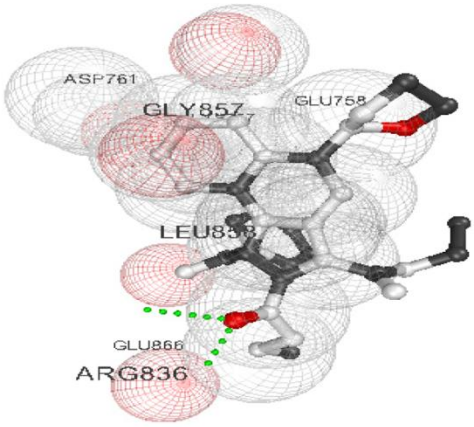

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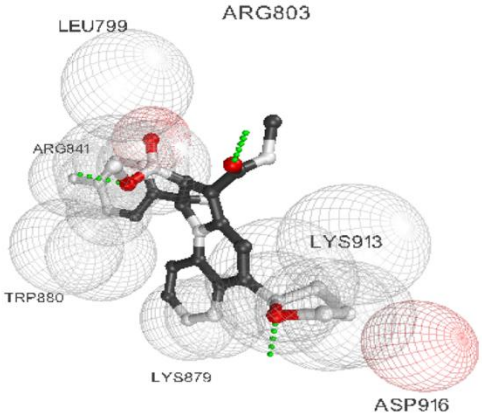

(n)