Synthesis and in Silico Studies of Novel Potent Kinase Inhibitors: 3-Indoloylquinoline Alkaloid

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ABSTRACT: *An exclusive approach towards the synthesis of indoylquinoline alkaloids has been illustrated, the present article describes the synthesis, in Platelet-derived growth factor receptor and silico molecular docking studies of a new compound 3-indolylquinoline-2,4-diol 4. The synthesis of 4 is initiated by a new, efficient, and solvent-free via a thermal Claisen condensation. The structures of the compounds are established using both spectral and analytical data. An in-silico PASS, Swiss ADME-assisted docking approach is found to be suitable for deriving and synthesizing effective receptor tyrosine kinase agents. Claisen ester condensation reaction resulted in the discovery of inexpensive and user-friendly solvents. Structures of the newly synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS (FTMS+PESI) analyses.*

KEYWORDS: *Claisen condensation; Indol-3-aceticacid; 3-(1H-indol-3-yl)quinoline-2,4-diol; Indole-3-methylacetate; Molecular docking; Protein kinase inhibitors.*

INTRODUCTION

Quinolines are important scaffolds in heterocyclic chemistry, and indolylquinoline alkaloids are present in many pharmacologically active substances. Indole and quinoline are two important classes of structural frameworks that are found in a huge number of natural products and pharmaceutically active compounds [1-4]. Compounds linking the both indole and quinoline rings are so-called indoloylquinoline identified to exhibit a wide variety of biological activities, including antibiotic, antimicrobial, and antifungal activities [5,6]. Antitumor, anticancer,

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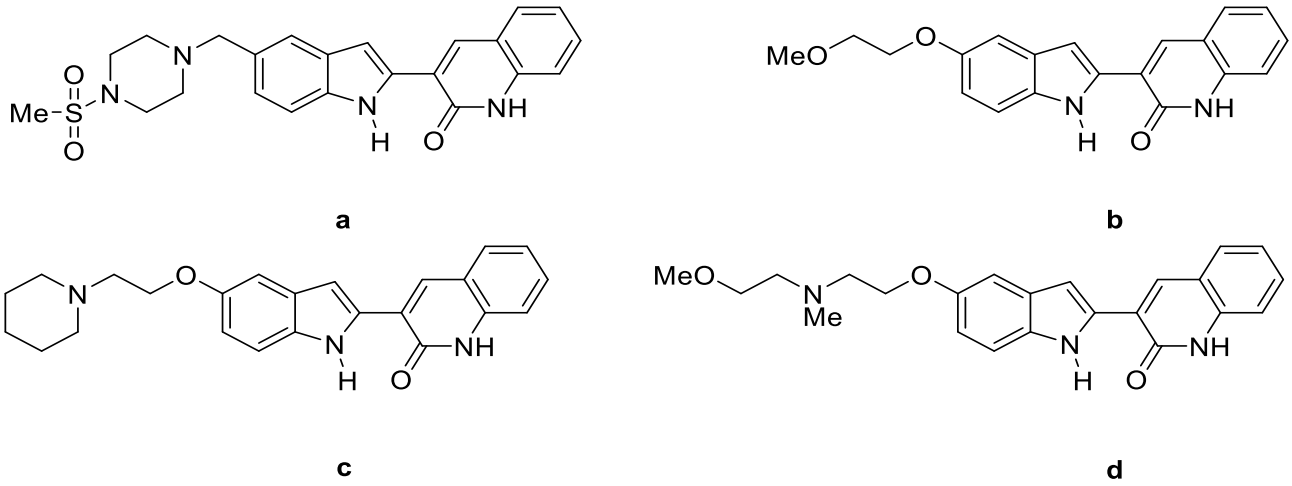


Fig. 1: Merck has identified KDR inhibitors for 3-indoloylquinoline a-d

andantimalarial [7-10]. While, different types of indoloylquinoline derivatives are known such as 2-indoloylquinoline, 3-indoloylquinoline and 4-indoloylquinoline in the literature are frequently found in many bioactive compounds. For example, 2-indolylquinoline analogues have also been reported as potential ant staphylococcal agents and antileishmanial activity of these indoloylquinoline derivatives both *in vitro* and *in vivo* [11]. Indoloylquinoline compounds destroy cancer at its roots by targeting cancer stem cells, so this is a promising approach for therapy. 3-((7-Ethyl-1H- indol-3-yl)-methyl)-2 -methylquinoline (EMMQ) shows a remarkable inhibiting for the growth of lung cancer cells through impairment of cellular mitochondria functions. EMMQ is used as a proliferation inhibitor of spheroids in culture. The findings support that EMMQ is an eligible approach to eradicate the minor, but tumorigenic lung cancer tumorspheres [12]. Merck has identified several potent and selective KDR inhibitors such as compounds [13-15], Fig. 1 (a-d).

Protein kinases serve as therapeutic targets for a range of clinical indications and represent the largest category of drug targets in current clinical trials, Platelet-Derived Growth Factor Receptor-beta (PDGFR-b) is expressed by Endothelial Cells (ECs) of tumour-associated blood vessels and regulates primarily early hematopoiesis. Human PDGFR-b is a novel therapeutic target for the treatment of glioblastoma. However, a major challenge of glioblastoma therapy is to overcome drug resistance, The key structural feature of these molecules is the indol-2-yl quinolin-2-one ring system bearing a substituent in the 5th position of the indole ring, Tyrosine kinases are a class of enzymes which are believed to play a critical role in signal transduction in several cellular functions and have been implicated in a wide range of diseases and conditions including angiogenesis, cancer, tumor growth, atherosclerosis, diabetic retinopathy, and inflammatory diseases to name a few [16-21]. The Kinase insert Domain Receptor (KDR) is a tyrosine kinase that has a high affinity for Vascular Endothelial Growth Factor (VEGF) and is believed to be a primary mediator of tumor-induced angiogenesis [22,23]. Compounds that inhibit, modulate, or regulate the KDR receptor are useful for the prevention and treatment of tumor-induced angiogenesis [24].

Recently, the synthesis of 2-(indol-3-yl)-3-nitriloquinolines *via* Friedlander quinoline synthesis using 3-cyanoacetylindoles possessing methylene group and ortho-amino arylketone has been described [25] and PEG-400 as a green solvent and it is catalyzed with polyphosphoric acid (PPA) to give novel types of quinolines containing both indoles and cyano functions in a one-step under thermal and microwave conditions. When the functional group doubles the product will appear as a dimer. A new method of C-alkylation of indoles by numerous Baylis–Hillman adducts and the one-pot reductive cyclization of C-alkylated indole offshoots produced from 2-nitro-Baylis–Hillman adduct to form indoloylquinoline derivatives [26]. Our earlier reports indoloylquinoline derivative, synthesis of 2,4-dihydroxy-3-(indol-2)-yl-quinoline is reported [27]. The importance of organic and medicinal chemists is to strategy and synthesize the new molecules having potent therapeutic values. The rapid

development of resistance to existing drugs generates a serious challenge to the scientific field. Consequently, there is a vital need for the development of new drugs has been revealed that minor modification in the structure of such heterocycles can lead to quantitative as well as qualitative changes in the biological activity [28-30].

In the present article, we have reported the design, synthesis and *in vitro* kinase inhibitor activities of 3-(1H-indol-3-yl) quinoline-2,4-diol, in the current drug discovery process, the potential of a novel compound is frequently studied initially through virtual tools. The possibility of a compound exhibiting useful drug-likeness is predicted from its molecular structure [36,37]. Prediction of bioavailability and bioavailability-related properties, such as solubility and lipophilicity, is important before the synthesis. Furthermore, we also describe *in silico* ADMET outline and PASS analyses of the compound.

EXPERIMENTAL SECTION

All chemicals and solvents are purchased from Fine and Merk Chemicals India. Melting points are uncorrected. Infrared spectral data is recorded using a Perkin-Elmer Paragon 1000 FT-IR spectrometer as potassium bromide discs unless otherwise indicated scanning 32 times from 4000 to 400 cm^{-1} at 4 cm^{-1} resolution. ^{1}H and ^{13}C NMR spectra are obtained in the $CDCl_3$ solvent on a Bruker (400 MHz) instrument. ^{1}H NMR data are recorded as follows: chemical shift measured in parts per million (ppm) downfield from TMS (d), multiplicity, observed coupling constant (*J*) in Hertz (Hz), proton count. Multiplicities are reported as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). 13C NMR (100 MHz) chemical shifts are reported in ppm downfield from TMS and identifiable carbons are given. GC-MS information Perkin Elmer, Mass Spectrometer Clarus 600 (EI), Clarus 680 GC is used in the analysis employed a fused silica column, packed with Elite- 5MS (5% biphenyl 95% dimethylpolysiloxane, 30 m × 0.25 mm ID × 250μm df) and the components are separated using Helium as carrier gas at a constant flow of 1 ml/min. The injector temperature is set at 260℃ during the chromatographic run. The 1μL of extract sample is injected into the instrument the oven temperature is as follows: 60°C (2 min); followed by 300°C at the rate of 10°C min^{-1}; and 300°C, where it is held for 6 min. The mass detector conditions are: transfer line temperature 240°C; ion source temperature 240°C; and ionization mode electron impact at 70eV, a scan time 0.2 sec, and a scan interval of 0.1 sec. The fragments are ranging from 40 to 600. All compounds are routinely checked by Thin Layer Chromatography (TLC) with Merck silica gel 60F-254 glass plates. In column chromatography, Merck silica gel 60-120 mesh, Petroleum ether, and ethyl acetate, as eluents, are utilized. Solvents and reagents are purified by literature methods. Petroleum ether refers to the hydrocarbon fraction of boiling range 60–80°C. Compounds are detected by short and long ultraviolet light and with iodine vapor.

Typical experimental procedure for the synthesis of indol-3-methylacetate (2)

Indole-3-acetic acid **1** (0.01 mol) is dissolved in absolute ethanol (15 mL), followed by adding 3 drops of con H_2SO_4. The mixture is then transferred to water bath at 70°C for 1 hour. After being subjected to the reaction conditions, after complete disappearance of starting material, the excess methanol is distilled out and cooled to room temperature. It is poured into ice-cold water; the precipitate is filtered and purified by column chromatography with the mobile phase of petroleum ether and ethyl acetate (95:5) to give semi-solid of indol-3-methylacetate 2.

Yield 2.60 g (85%); Semi-Solid; IR (KBr, υ_{max},cm^{-1}): 3335, 3052, 2979, 1716, 1458, 1375; ^{1}H NMR (500 MHz, DMSO-*d6*): δ 11.54 (br s, 1H, N-H), 7.98 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.67 (t, 1H, Ar-H), 7.63 (br s, 1H, Ar-H), 7.29 (t, 1H, Ar-H), 7.37 (d, 1H, Ar-H, *J* = 8.0 Hz), 2.71 (s, 3H, $-OCH_3$), 2.50 (s, 2H, Indol-CH_2) ; ^{13}C NMR (125 MHz, DMSO-*d6*) δ 176.1 139.6, 132.7, 130.3, 129.7, 122.7, 122.0, 118.5, 115.2, 57.7, 30.3; HRMS (EI^{+}) m/z: $[M+H]^{+}$ calcd for $C_{11}H_{11}NO_2$ =189.21 found: 188.2474.

Synthesis of 3-(1H-indol-3-yl)quinoline-2,4-diol (4)

A mixture of methylantharanate **3** (1.51g, 0.1 mole), indol-3-methylacetate **2** (1.89.g, 0.1 mole) and NaH (0.50 g) are heated to reflux at 140°C for 6 hours. Then the reaction is being monitored by TLC. The condensed material is then poured into ice-cold water; the precipitate is extracted with ethyl acetate, concentrated and purified through column chromatography with petroleum ether and ethyl acetate mixture (90:10), to afford the title product 4

as a yellow crystals, 75 % yield; FT-IR (KBr, ν_{max}, cm^{-1}): 3453, 3228, 2919, 2849, 1679, 1621, 1541; ^{1}H NMR (500 MHz, DMSO-*d6*): δ 12.45 (br s, 1H, indol-N-H) 12.01 (br s, 1H, quinoline-OH), 11.48 (br s, 1H, quinoline-OH), 8.78 (s, 1H, indol-H), 8.27 (dd, 1H, quinoline-H) 7.78 (dd, 1H, *J* = 7.5 Hz, quinoline-H), 7.37 (dd, 1H, *J* = 8 Hz, indole-H), 7.69 (t, 1H, quinoline-H), 7.51 (t, 1H, quinoline-H), 7.32 (dd, 1H, *J* = 9 Hz, indol-H) 7.29 (dd, 1H, quinoline-H), 7.19 (t, 1H, indol-H) ; ^{13}C NMR (125 MHz, DMSO-*d6*): δ 160.6, 158.6, 149.9, 140.1, 134.1, 133.9, 130.1, 129.4, 128.6, 124.1, 122.9, 118.9, 117.7, 115.9, 115.8, 115.1, 105.9; GC-MS: m/z [M] 276 (48%).

Pharmacological/biological assays

Prediction of activity spectra for substances (PASS)

We have used PASS (Prediction of Activity Spectra for Synthesis of compound 4, an available server at for computational screening of possible biological effects. PASS online provides simultaneous predictions of a wide range of biological activity based on the structure of organic compounds. The PASS activity is predictable about Pa (probable activity) and Pi (probable inactivity). Structures with Pa greater than Pi are the only compounds considered for a particular pharmacological activity [31].

ADME analysis

ADME analysis is carried out using the SWISS ADME and molinsperation predictor for the present investigation. This is a free web server tool to evaluate the ADMET properties, like physicochemical properties, water solubility (log S), skin permeability (log Kp), synthetic Accessibility Score (SA), percentage absorption, pharmacokinetics, drug-lead likeness and medicinal chemistry friendliness properties of drugs molecules. The importation analysis of molecular weight< 500, 5 Hydrogen Bond Donors (HBDs), 10 Hydrogen Bond Acceptors (HBAs), and < 10 Rotatable Bonds (RBs). The grade analysis results on the lipophilicity and hydrophilicity of these molecules by integrating results obtained from several log P and S prediction programs called ILOGP, XLOGP3, WLOGP, ESOL, and SILICOS-IT. log P, a portion of the lipophilicity of a molecule is the logarithm of the ratio of the concentration of a drug substance in two solvents in a unionized form, the lower the log P value, the stronger the lipophilicity is better. The aqueous solubility of a compound especially affects its absorption and distribution characteristics, low water solubility often leads to bad absorption, and therefore, the general aim is to avoid poorly soluble compounds. log S is a unit expressing solubility, and it is the 10-based logarithm of the solubility measured in mol/L. The distribution of log S between -1 and -4 will be optimized for better absorption and distribution of drugs in the body [32-34].

Molecular docking study

Before the docking experiment, all the synthesized chemical structures are sketched in Chemoffice 16.0 tool and accessed in mol2 format. Furthermore, UCSF Chimera 1.10.1 tool is employed for energy minimization of ligand, separately, having default parameters such as steepest descent steps 100 with step size 0.02 (Å), conjugate gradient steps 100 with step size 0.02 (Å) and update interval is fixed at 10. Finally, Gasteiger charges are added using a Dock Prep in ligand structure to obtain the good structure conformation. A molecular docking experiment is employed on all the ligands, 4, against (3QRJ) human abl1 kinase by using the virtual screening tool Autodock with VINA Wizard approach. 20 The grid box parameters values in VINA search space (X= 4.737902, Y= -12.433707 and Z= 28.428195) are adjusted with default exhaustiveness value=8 to maximize the binding conformational analysis. The synthesized ligand is docked separately against target protein. In all docked complexes, the ligands' conformational poses are keenly observed to obtain the best docking results. The generated docked complexes are evaluated on the basis of lowest binding energy (kcal/mol) values and Structure-Activity Relationship (SAR) analyses. The three-dimensional (3D) graphical depictions of all the docked complexes are accomplished by Pymol and Discovery Studio (2.1.0) [35-37].

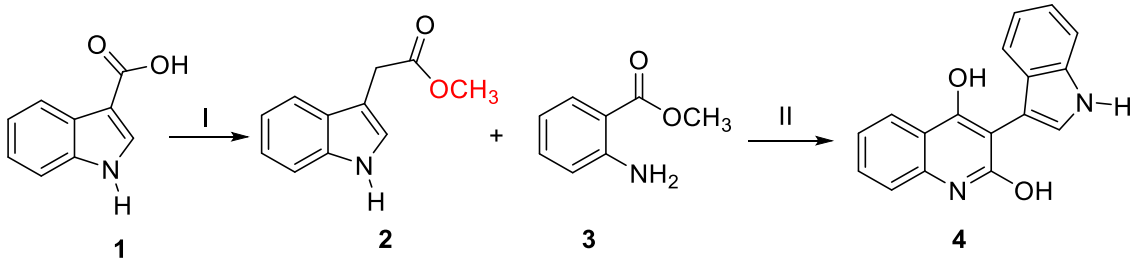
RESULTS AND DISCUSSIONS

Synthetic Chemistry

Synthesis and characterization of 3-(1H-indol-3-yl)quinoline-2,4-diol 4

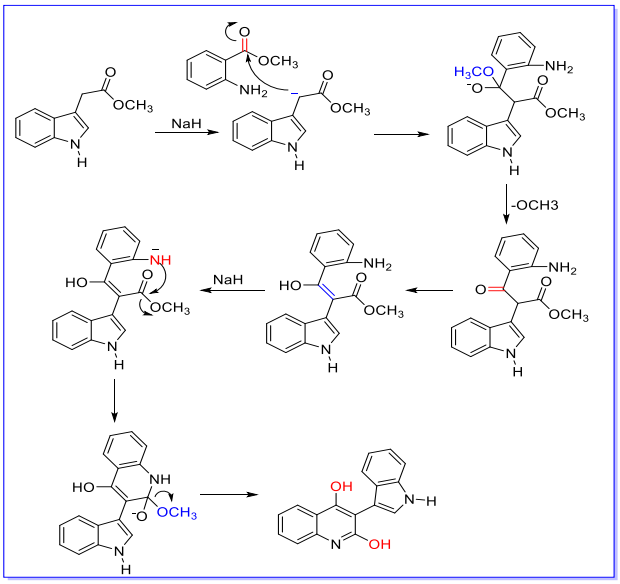
We report herein on a conventional approach to 3-indolylquinoline typically relies upon Claisen condensation reaction.

The planned 3-indolylquinoline is synthesized through a two-step protocol depicted in Scheme 1. The first step in the synthesis involved effective Fischer esterification of indole-3-acetic acid 1 with a mixture of methanol and a catalytic amount of conc. H_2SO_4; is refluxed at 70°C to give indol-3-methylacetate 2. The condensation reaction



Scheme 1: Outline for the synthesis of 3-(1H-indol-3-yl)quinoline-2,4-diol. Reagents and Conditions: (I) CH_3OH, con H_2SO_4, reflux for 100˚C, 1h. (II) NaH, reflux for 140˚C, 4 hours

of methyl-2-aminobenzoate 3 with indol-3-methylacetate 2 by Claisen condensation reaction in the presence of sodium hydride as a strong base to obtain the desired 3-(1H-indol-3-yl)quinoline-2,4-diol 4 in 75 % yield. Compounds 2 and 4 are purified by recrystallization from appropriate solvents. The molecular structures of these derivatives are well established by IR, EI-MS, ^{1}H NMR, and ^{13}C NMR spectral data. The structural characterization of one of the lead compounds is discussed hereby in detail. Compound 4 is acquired as a light-yellow solid with 81% yield. Its molecular formula, $C_{11}H_{11}NO_2$, is recognized by CHN analysis data and molecular mass and justified by the molecular ion peak in its EI-MS at m/z 276. The mass fragmentation pattern is also supported to erect the said molecular formula. Moreover, counting the number of protons in its ^{1}H NMR spectrum and the carbon resonances in its ^{13}C NMR spectrum also supplemented the assignment of molecular formula. The prominent absorption bands in IR spectrum disappeared ester at 1716 cm^{-1} (C=O stretching), appeared at 3453cm^{-1} (OH of aromatic ring), 3228 cm^{-1} (N-H stretching), 2919 (-CH- aromatic stretching), 1679 (C=N stretching) and 1541 (C=C stretching of aromatic ring). The most downfield signals in its ^{1}H NMR spectrum δ 12.45 (s, 1H, indol N-H), 12.01(br s, 1H, quinoline-OH) and 11.48 (br s, 1H, quinoline-OH) are assignable to two protons. the heterocyclic group in the molecule is obvious by its isolated signals at δ 8.78 (s, 1H, indol-C_2-H), 7.78 (dd, 1H, *J* = 7.5Hz, quinoline-C_5-H), 7.37 (dd, 1H, *J* = 8 indol-C_4-H), 7.69 (t, 1H, quinoline-C_5-H, *J* = 7.5), 7.51 (t, 1H, quinoline-C_6-H, *J* = 8), 7.32 (dd, 1H, *J* = 9, indol, C_6-H) 7.29 (dd, 1H, *J* = quinoline, C_7-H), 7.19 (t, 1H, indol-C_4-H), disappearance of methoxy and methylene singlet proton is 2.72 and 2.50; are attributed to the indole-substituted quinoline unit in the molecule. ^{13}C NMR further supports the structure; disappearances of the ester carbonyl group at δ 176 and aliphatic regional



Scheme 2: The possible reaction mechanism is outlined for the synthesis of 3-(1H-indol-3-yl)quinoline-2,4-diol 4

carbon at δ 30.3 and 57.7. An important evidence for the convenience of 4 moiety is by observing m/z 276 on the mass spectra; The above data is provided to confirm the compound as 3-(1H-indol-3-yl)quinoline-2,4-diol 4.

The formation of 3-(1H-indol-3-yl)quinoline-2,4-diol 4 can be explained by the Claisen condensation mechanism. The α-hydrogen of ester at 2 is abstracted by NaH to form an enolate of 2, which then attacks the carbonyl of methyl 2-aminobenzoate 3, followed by the removal of ethoxide ions to give the corresponding ketone. The acidic proton between the ester and ketone carbonyls is then removed to afford the enol derivative. Another deprotonation has happened in this reaction, but this time on the NH_2 group, which can make the anion form (NH-) that is considered more reactive towards nucleophilic addition. This is followed by the removal of the methoxy group to provide the desired product 4.

Table 1: The activity spectrum of 3-(1H-indol-3-yl)quinoline-2,4-diol 4, pa represents probability to active and pi represents probability of being inactive

S. No	Activity name	Pa	Pi
1	Thioredoxin inhibitor	0,720	0,009
2	Serum-glucocorticoid regulated kinase 1 inhibitor	0,553	0,004
3	Antineoplastic	0,594	0,046
4	Nitrate reductase (cytochrome) inhibitor	0,562	0,033
5	Nicotinic alpha6beta3beta4alpha5 receptor antagonist	0,589	0,075
6	Nicotinic alpha2beta2 receptor antagonist	0,566	0,057
7	Kinase inhibitor	0,532	0,029
8	(S)-6-hydroxynicotine oxidase inhibitor	0,525	0,028
9	Acute neurologic disorders treatment	0,539	0,061

Pharmacology/Biology

Biological activity spectrum PASS analysis

The biological activity spectra of the synthesized compound are determined using an online server of PASS. A synthesized compound 4 showed the highest Pa for Kinase inhibitor activities 0,525. (Table 1).

ADME analysis

The predicted chemo-informatic properties are evaluated by computational tools, *in-silico* studies clearly indicate that the compounds have drug-like candidate properties with no violation of any of the drug-likeness rules discussed above. It is interesting to note that the results of the SWISS ADME and Molinspiration predictor values of log P, molar refractivity and the total polar surface area in these molecules are in excellent agreement with the most important rules of drug-likeness.

The predicted chemo-informatic properties are evaluated by computational tools. Results exposed that compound 3-(1H-indol-3-yl) quinoline-2,4-diol **4** have the better predicted value of molecular weight 276.29 (g/mol), which is within the range value (< 500 g/mol) which higher molecular weight compound than the borderline value. Hydrogen bond acceptor and donor, logP, polar surface area (A^2), and molar volume (A^3). Though this compound exhibited a good hydrophilic–lipophilic balance and the same predicted bioavailability, high lipophilicity is expected to show decent GI absorption. In addition, 69.14 $Å^2$ calculated the total polar surface area (TPSA) since it is another key property that is related to drug bioavailability. Thus, passively absorbed molecules with TPSA >140 are thought to have low oral bioavailability, Furthermore, the molecular polar surface area (PSA) is a very useful parameter for drug transport properties, the molecule is defined as the surface sum over all polar atoms, primarily oxygens, nitrogen's and attached hydrogen atoms. This parameter has been shown to correlate very fine with the human intestinal absorption Caco-2 monolayer permeability and blood-brain barrier penetration. The PSA parameter is commonly used for a drug's optimization ability to permeate cells. Prior research data has shown that the standard value of PSA (< 89 A^2). Furthermore, Lipinski's rule RO5 of result 0 violation has shown that compound **4**, possesses a good molecular weight (g/mol). Two hydrogen bond acceptor and hydrogen bond donor values two, log P 2.28 which significantly justified their drug-likeness behavior, which is justifiable with the standard values. The RO5 deviation (Mol. Wt≥500 g/mol; HBD≥ 5; HBA > 10; and logP≥ 5). drug-likeness score is an amalgam of a complex balance of several molecular properties and structure features that determine the behavior of a molecule as a drug. 0.55 is a good drug score value, thus be considered a suitable drug candidate against kinase inhibitor activities. The results obtained from the Swiss ADME and Molinspiration search engine are listed in Table 2**.**

The boiled-egg diagram analysis indicates that the compound is strong within the permissible range of standard drugs, (Fig. 2) blue dot indicates cannot be affected by the P-glycoprotein of the CNS system by P-glycoprotein, point located in Boiled Egg yolk is a molecule passively permeate through the Blood–Brain Barrier (BBB). In the current study, the synthesized ligand and its complexes is initiated to be in good pact with the given criteria and can be said to possess good bioavailability.

Molecular docking

The molecular docking is a valuable technique in computational chemistry and medicinal chemistry to

Table 2: Physicochemical descriptors and ADME parameters[a]

M.W g/mol	R-B	H-A	H-D	TPSA Å^2	MR	W log P	ESOL log S	BBB permeant	log Kp cms^{-1}	Lipinski violations	PAINS alerts	GI absorption	Synthetic accessibility
276.29	1	3	3	69.14	83.08	2.28	-4.41	Yes	-5.45	**0**	**0**	High	2.34

[a] R bond =Rotatable bond, H-A = Hydrogen bond acceptor, H-D =hydrogen bond donor, TPSA = topological polar surface area, BBB = blood brain barrier, log P = lipophilicity, log S = water solubility, log Kp = permeability coefficient, PAINS = pan-assay interference structure.

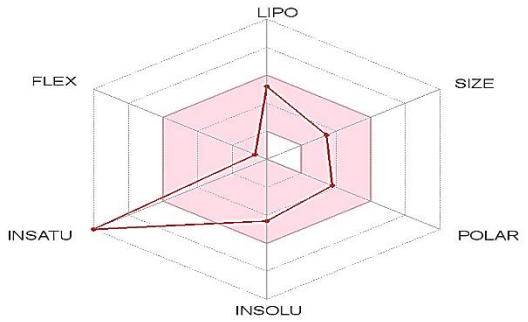


Fig .2: Bioavailability radar graph of 3-(1H-indol-3-yl) quinoline-2,4-diol 4 (pink area reflects the allowed values of drug likeness properties of the molecule)

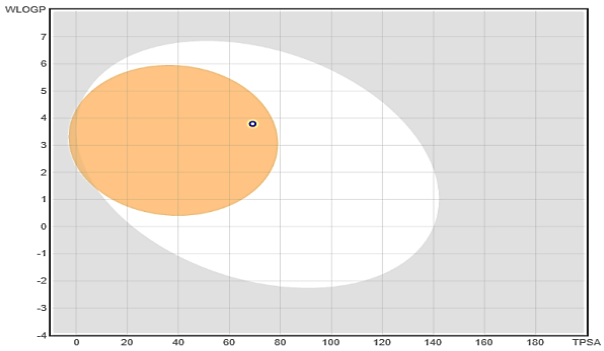


Fig 3: ADME properties of compound 3-(1H-indol-3-yl) quinoline-2,4-diol by graphical representation (boiled-egg)

acutely analyses ligand recognition, and it has led to important breakthroughs in drug discovery and design. Molecular docking methodology explores the binding mode and affinity of a small molecule within the binding site of the receptor target protein. The docked ligands are ranked according to their binding affinity in ligand–receptor complexes (Fig. 3). The synthesis of compound **4** is to evaluate their potential to transferase inhibitor human abl1 kinase. Molecular docking is performed on a test synthesized compound 3-(1H-indol-3-yl)quinoline-2,4-diol, against the (3QRJ) human abl1 kinase to identify the ligand– interaction protein.

The docking score -8.6 due to the tested ligand determined that the prepared admixtures possessed the potential for interaction with one or more amino acids in the active site (binding pocket) of the receptor. The docking result shows that the two hydrogen bonds, two electrostatic bonds and four hydrophobic interactions are observed in the synthesized docked complex. Both oxygen molecules of amine groups in **4** formed two conventional strong hydrogen bonds with Glu286:OE2, Asp381:O with bond lengths of 3.78, 3.61Å (3QRJ human abl1 kinase Main protease) respectively. Similarly, four Pi-Alkyl hydrophilic interactions is observed between the quinoline ring and Ile293, Val289, Met290 another Val289 having bond distances of 4.66, 5.02, 4.94, 4.86 Å. Two positive Pi-Cation electrostatic bond is observed between quinoline ring Glu286:OE1 another Glu286:OE2 having bond lengths of 4.95 and 4.07Å. Hydrogen bonds play an important role in molecular docking because they help to stabilize and strengthen the docked enzyme–inhibitor complex. However, for hydrophobic interactions, distances vary up to 5Å. Synthesized compounds showed reasonable to good docking auto dock binding energies -8.6 kcal mol^{-1} values of the inhibitor compound are found reliable.

CONCLUSIONS

In conclusion, we have developed a new convenient, facile and selective method for the direct synthesis of indoloylquinoline alkaloid using a Claisen condensation of indole-3-ester with methylantharanate. methylantharanate and indole-3-aceticacid. The present technique is more environmentally benign than the generally practiced ester condensation. The procedure offers several advantages including mild reaction conditions, operational simplicity, inexpensive reagents, and rapid reaction time. Kinase inhibitor drugs to evaluate and their binding affinities with kinase receptor (PDB ID: 3QRJ) by molecular docking. Our results show that compound **4** molecules showed promising *in silico* results, as indicated by their significant

Table 3: The binding affinity values of different poses of compound 3-(1H-indol-3-yl)quinoline-2,4-diol predicted by autodock Vina

Mode	Affinity (kcal/mol)	Distance from the best mode	
		RMSD 1.b.	RMSD u.b.
1	-8.6	0.000	0.000
2	-8.6	1.178	2.115
3	-8.3	1.564	5.849
4	-7.9	1.098	1.975
5	-7.8	1.883	6.096
6	-7.8	1.247	6.189
7	-7.8	1.703	2.892
8	-7.6	1.622	6.238
9	-7.6	1.846	6.129

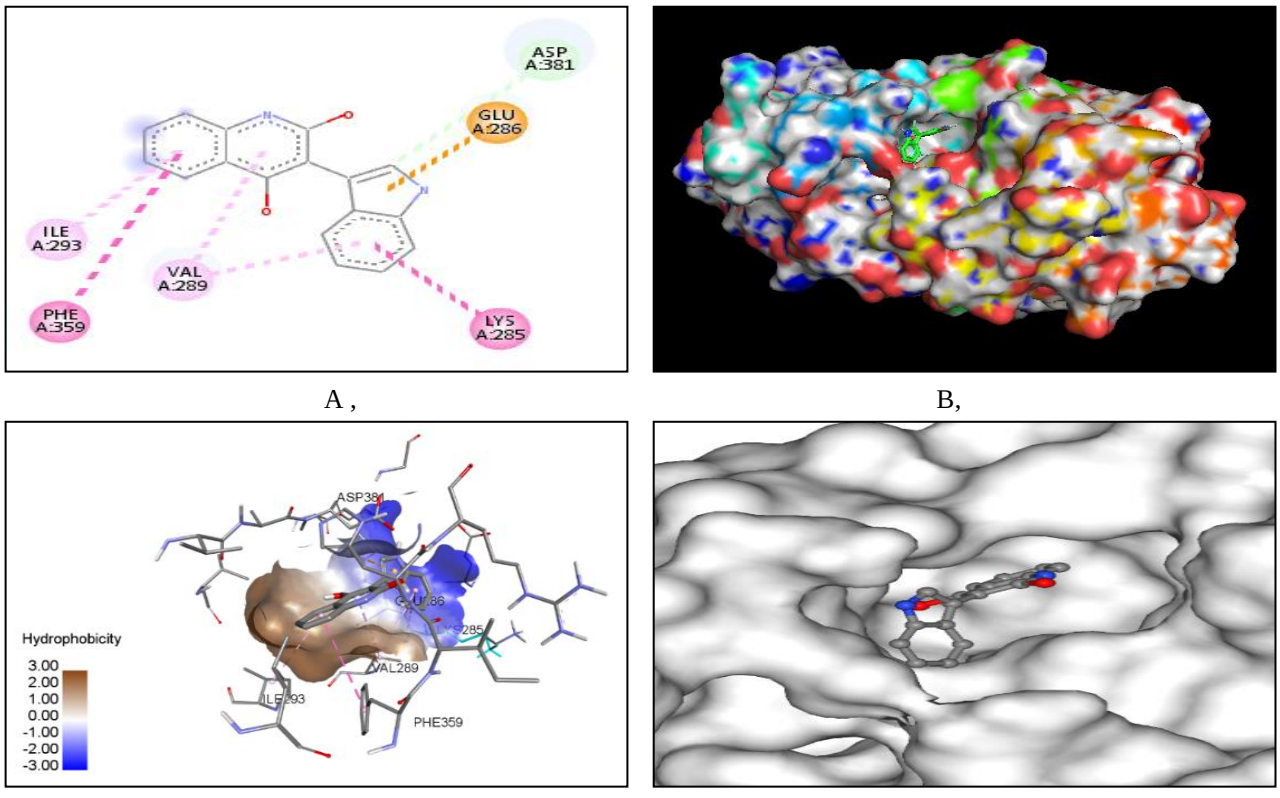


Fig 4: (A) The docked ligand 3-(1H-indol-3-yl)quinoline-2,4-diol 4 at the same catalytic site receptor, (B) The docking poses of 3-(1H-indol-3-yl)quinoline-2,4-diol in the binding site of the human abl1 kinase receptor (PDB ID: 3QRJ (C) interaction with the ligand 4 the hydrophobic surfaces of the receptor kinase inhibitor, (D) 2D Docking poses of compound 4 into 3QRJ the protease

scoring functions and high protein–ligand interaction energy, which simultaneously predicted the activity of the test compound. *The in silico* ADME reporting, toxicity, drug-likeness, drug scoring results, PASS analysis, and kinase inhibitor activities suggested that the compound is a promising lead for the development of a selective, potent kinase inhibitor.

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