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ORIGINAL ARTICLE

Molecular explorations of substituted 2-(4-phenylquinolin-2-yl) phenols as phosphoinositide 3-kinase inhibitors and anticancer agents

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Abstract
Purpose Substituted 2-(4-phenylquinolin-2-yl) phenols (PQPDs) emerged as the inhibitors of phosphoinositide 3-kinase (PI3K) and anticancer agents.
Method PI3K inhibition was assessed by competitive ELISA. Anticancer activity was evaluated against breast cancer (MCF-7), skin cancer (G-361), and colon cancer (HCT 116) cell lines.
Results In PI3 Kinase assay, PQPDs 4c, 4d, and 4k were inactive with IC_{50} >5 μM. IC_{50} for 4a, 4b, 4f–h, and 4j was ≥0.05 μM. Rest PQPDs IC_{50} was <1.0 μM. Anticancer activity found selective toward breast cancer (MCF-7); 4a, 4b, and 4j were showed excellent inhibitory (73.95, 68.36, and 70.06%) and IC_{50} 1.16 μM (4a), 2.07 μM (4b), 1.021 μM (4f) and 1.981 μM (4j) while the standard (Doxorubicin) found with IC_{50} 1.812 μM (72% inhibition). PQPDs were docked into the active site of PI3 Kinase p110α (PDB ID: 2RD0). Docking results suggested the hydrophobic interactions in PI3K binding pocket conquered affinity of the most favorable binding ligands [4a, 4b: inhibitory constant (ki) = 53.33, 41.23 pM].
Conclusion PI3K assay and cancer cell line experimental results ensured that the inhibitory and anticancer activity potentials of PQPDs are more selective toward breast cancer treatments. PQPDs 4a, 4b, 4f, 4g, and 4j were displayed potent PI3 Kinase and anticancer activities. SAR studies demonstrated PQPDs as the PI3K precise inhibitors with the impending to treat various cancers.

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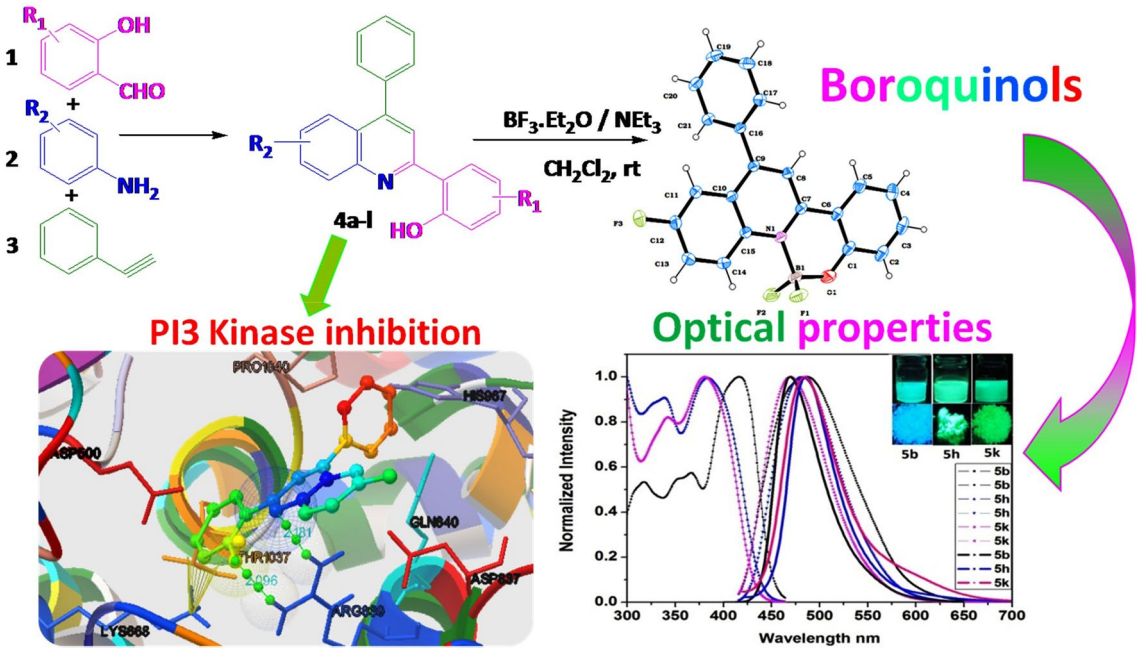
Graphical Abstract



Keywords Phosphoinositide 3-kinase (PI3K) · ELISA · Anticancer · SAR · Molecular docking · MCF-7 cell lines

Introduction

Quinolines have demonstrated with a wide range of anticancer activities [1–3]. 2-phenylquinoline and 2-phenylquinolone derivatives have already been established as potent antitumor agents [4, 5]. In their derivatives, quinoline ring takes significant responsibility in the mechanism of actions which are highly involving in the cancer developments like seizing cell cycle, cell migration distribution, angiogenesis inhibition, apoptosis, and in the nuclear receptor responsiveness modulations [6–8]. For instance, imidazoquinoline skeleton in the 1,4-disubstituted imidazo[4,5-*c*]quinolines was found with excellent anticancer activity [9]. 2-phenyl quinoline comprising [(2-aminoethyl)aminomethyl] showed the capability of interpolation into double-stranded DNA which is an indispensable intention for cytotoxicity [10].

Phosphoinositide 3-kinases (PI3Ks) are the vital regulators of apoptosis and cellular functions involved in the cancers like cell growth, proliferation, differentiation, motility, survival, and intracellular trafficking [11, 12]. Numerous PI3 Kinase inhibitors (small molecule inhibitors) at present go for clinical trials in the interest of various cancer treatments [13, 14]. PI3Ks are the signal transducer enzymes accomplished with phosphorylating the 3 position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns) [15–17]. Mutations are frequent in the PI3K pathway of breast cancer, and the p110 catalytic subunits (p110α and p110β isoforms) of PI3Ks are generally expressed in cells; especially, class IA PI3 Kinase p110α is mutated in several cancer types [18, 19]. PI3K pathway is often abnormally turned on with mutations taking place in breast cancers [20, 21]. Consequently, the great involvement of the PI3 Kinase action potential to cellular alterations and the progress of breast cancer were understood. In the present study, substituted 2-(4-phenylquinolin-2-yl) phenols (PQPDs) 4a–l was evaluated for their PI3Ks inhibitory and anticancer properties. PI3Ks enzyme inhibition assay and anticancer studies on breast cancer (MCF-7), skin cancer (G-361), and colon cancer (HCT 116) cell lines were executed. To get more insights into the binding mode, a molecular docking study was carried out (with PI3 Kinase p110α, PDB ID: 2RD0) preliminary headed for animal model evaluations.

Materials and method

Chemical compounds

Phenylquinoline phenol derivatives (PQPDs) 4a–l was well established and characterized in our previous report [22]. Compounds were carefully packed and preserved under 4 °C for future biological studies. Complete investigational procedures and structural depiction data along with spectra and PQPDs (4a–l) structures are unveiled in the Supporting Information (SI). The compound solubility was determined prior to use for the biological assay. Compounds were

dissolved in DMSO (dimethysulfoxide) in the 1:10 ratio. From these dilutions, 20–250 µg/mL concentration solutions were prepared. The IC_{50} values obtained (in µg/mL) were calculated/converted in µM and reported.

PI3 Kinase activity assay

PI3 Kinase assay was carried out as reported with slight modifications [23]. Glutathione-coated 96-well plate was used to execute the assay. The kinase and the inhibitor were pre-incubated for 10 min prior to adding PIP2 (phosphatidylinositol biphosphate) substrate. 5 µL/well of 5× kinase reaction buffer and 5 µL/well of PIP2 substrate were added. Distilled H_2O to each well below, to make up for a final 25 µL/well, was employed, and the reaction mixture was incubated at RT for 1 h. 25 µL/well of biotinylated phosphatidylinositol biphosphate (b-PIP3)/EDTA working solution excluding the buffer control wells and 25 µL/well 1× TBS (Tris-buffered saline) to the buffer control wells were added. Then, 50 µL/well of GRP1 (general receptor for phosphoinositides 1) working solution was added to all wells and incubated at RT for 1 h. The wells are washed at least 4 times with 200 µL/well 1× TBST (Tris-buffered saline and Tween 20), and 50 µL/well SA-HRP working solution was added and incubated at RT for 1 h; 200 µL of 1X TBST per well and then 2 times with 200 µL of 1× TBS per well was added. Finally, 100 µL of the substrate TMB per well developed in the dark for 5–20 min then read at 450 nm. The relative % to b-PIP3 was calculated using the following formula,

$$\%\ \text{inhibition} = \frac{\text{OD of samples (buffer, kinase and inhibitors)}}{\text{OD of B - PIP3 average}} \times 100.$$

Cell lines preparation for assay

The early passage of proposed cancer cell lines used in this study was developed and cultured as previously described [24, 25]. All cancer cells were cultured in DMEM (Dulbecco's modified Eagle's medium) supplemented with 10% fetal bovine serum (FBS), (100U) 20 µg/ml penicillin, and 100 µg/ml streptomycin. They were subcultured by removing existing medium and adding fresh 0.25% trypsin–0.53 mM EDTA for several minutes, and then, trypsin was removed and the culture sit at 37 °C for 10–15 min. Fresh medium was added, aspirated, and dispensed into new flasks. Incubation was carried out at 37 °C in an atmosphere of 5% CO_2. For the assay, 1 ml of homogenized cell suspension was poured in each well of a microtitre plate and kept in a desiccator. After 48 h of incubation, the cells were observed under the inverted microscope. 0.05 ml of the drug was dissolved in 4.95 ml of DMSO to get a working concentration of 1 mg/ml. The working concentration was prepared freshly and filtered through 0.45-micron filter before bioassay.

MTT assay for antiproliferation/anticancer evaluations

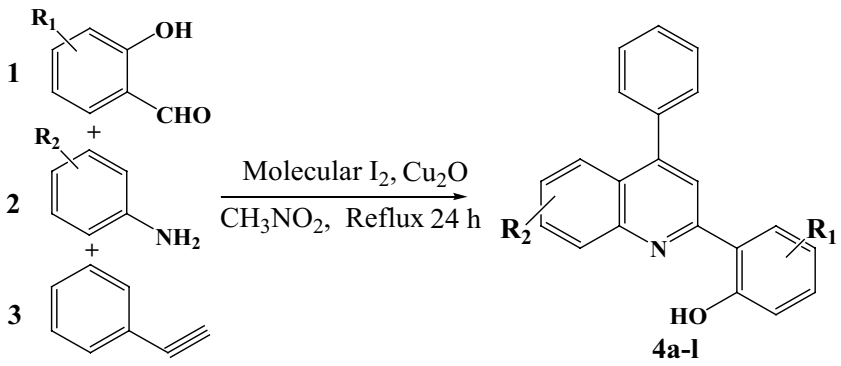
The anticancer activity of PQPDs (4a–l) on various cancer cell lines was determined by the MTT (3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl tetrazolium bromide) assay as we previously reported [24, 25]. Doxorubicin (DOX) was used as the standard drug in this study since it is generally used in the treatment of many types of carcinoma (solid tumors) and soft tissue sarcomas including blood cancers, like leukemia and lymphoma [28]. Approximately 5000 cells were seeded in 96-well, flat-bottom titer plates and incubated for 24, 48, and 72 h at 37 °C in 5% CO_2 atmosphere. Different concentrations of PQPDs (4a–l) (50–500 µg/mL) were added and incubated further for various time periods. After completion of incubation, the medium was removed. The wells were washed with PBS; 100 µL of the working MTT dye in DMEM (Dulbecco's modified Eagle's medium) media was added and incubated for 2 h. MTT lysis buffer (100 µL) was added, and incubation continued for 4 h more. The absorbance was measured at 570 nm, and the cell viability was calculated using the following formula,

$$\text{Cell viability}\ (\%) = \text{Mean OD/Control OD} \times 100\%.$$

Molecular docking studies

Docking study performed in order to get more insight into the binding mode of the PQPDs into the binding pockets of PI3 Kinase. Autodock4.2.6 and Autodock Tools (ADT)1.5.6. and the Arguslab version 4.0.1 were used for the docking studies. All strategy and measures for docking studies were followed and customized accordingly to our previous reports [25–27]. Their 3D atomic coordinates of PQPDs (4a–l) were created using ACD/Labs—Chemsketch 12.0 software. PQPDs (4a–l) geometries were cleaned and generated as the corresponding *pdb.* ligand files. Three-dimensional crystal structure of the PI3 Kinase (PDB ID: 2RD0, Sup. Figure 25, p31) retrieved from the protein data bank (PDB) (Source: www.rcsb.org/pdb/). The receptor protein and ligands in the docking studies were treated using the united-atom approximation, only polar hydrogens were added to the protein, and Kollman united-atom partial charges were assigned. Unless stated otherwise, all waters were removed [29]. The *pdbqt* files for protein and ligands preparation and generating the grid box were completed using graphical user interface program AutoDock Tools (ADT). AutoGrid was used for the preparation of the grid map using a grid box. The grid size was set to 60 × 60 × 60 *xyz* points with a grid spacing of 0.375 Å, and grid center was designated at dimensions (*x*, *y*, and *z*): 0.885, 0.964, and 0.865. The ligand PQPDs (4a–l) were docked into the active sites of cancer-associated PI3 Kinase (PDB ID: 2RD0). Statistical mechanical analysis for the ligand PQPDs (4a–l) was analyzed, and the lowest binding

Scheme 1 Synthesis of substituted 2-(4-phenylquinolin-2-yl) phenol (4a–l)



energy, ligand efficiency, and the inhibitory constant (ki) values were extracted. Molecular interactions like hydrogen bonding, π–π interaction, and π–cation interaction results were analyzed and validated for structure–activity relationships.

Statistical analysis

All results were expressed as percentage increase or decrease with respect to control values. Results were also compared by one-way ANOVA and Dunnett's post-test. GraphPad Prism version 6.07 for Windows, GraphPad Software, San Diego California, USA, www.graphpad.com, was used for statistical analysis. A difference was considered statistically significant if $p \leq 0.05$. The 50% inhibitory concentration (IC_{50}) was calculated from the dose–response curve obtained by plotting percentage inhibition versus concentrations.

Results and discussions

Functional group investigations of substituted 2-(4-phenylquinolin-2-yl) phenol (4a–l)

PQPDs (4a–l) were synthesized by refluxing the corresponding aniline, salicylaldehyde, and phenylacetylene in nitromethane solution in the existence of iodine and cuprous oxide (Cu_2O), which gave moderate to good yields, and the substituted 2-(4-phenylquinolin-2-yl)phenol derivatives (PQPDs) were achieved as revealed in Scheme 1 (Ref. [22] for more details). A two-step formation, including an imine development and a 1,2-cycloaddition, for the proposed structures of PQPDs (4a–l), was observed (Sup. p-2 Fig. 1).

Table 1 depicts the substituted functional groups of PQPDs (4a–l) in order to understand the most probable anticancer potent moiety in which the functional group involved. –CHO and the halogens are the major constituents which are mostly playing a significant role in the dissimilarity of the proposed activities of PQPDs (4a–l), while the aromatic arene, azaarene, heteroarene, and phenol ring were the common components throughout the PQPDs (4a–l).

PI3 Kinase assay

A competitive ELISA colorimetric assay was conducted with ATP against the active (p110α/p85α) PI3 Kinase. The conversion of PtdIns-P2 to PtdIns-P3 was measured by adding PtdIns-P2, ATP, and the active enzyme along with the PQPDs to a buffered solution. The kinase and the inhibitor were pre-incubated for 10 min prior to adding PIP2 substrate. Wortmannin was used as a control for this assay, and it was evaluated in DMSO at 1 and 10 nM final concentrations. A primary diagnostic screen of the PQPDs against PI3-K p110α was carried out, and the results were noted (Table 1 Sup.). Compounds 4c, 4d, and 4k were inactive, all possessing IC_{50} values >5 μM.

The IC_{50} for compounds 4a, 4b, 4f–h, and 4j was $a \geq 0.05$ μM range. Rest compounds IC_{50} was in the <1.0 μM range. As depicted in Fig. 1, the calculated percentage

Table 1 Substituted functional groups in PQPDs (4a–l)

S. no.	Category	Functional group	Entity
1	Aromatics	Aniline	4a–l
2	Aromatics	Arene	4a–l
3	Aromatics	Azaarene	4a–l
4	Aromatics	Benzene ring	4a–l
5	Aromatics	Heteroarene	4a–l
6	Aromatics	Phenol	4a–l
7	CHO-	Alkanol	4a–l
8	CHO-	Ether	4c, 4j
9	Halogen-	Aryl bromide	4e, 4i
10	Halogen-	Aryl chloride	4g, 4f
11	Halogen-	Aryl fluoride	4h
12	Halogen-	Aryl halide	4e, 4f, 4g, 4h, 4i
13	Halogen-	Leaving group	4e, 4f, 4g, 4i

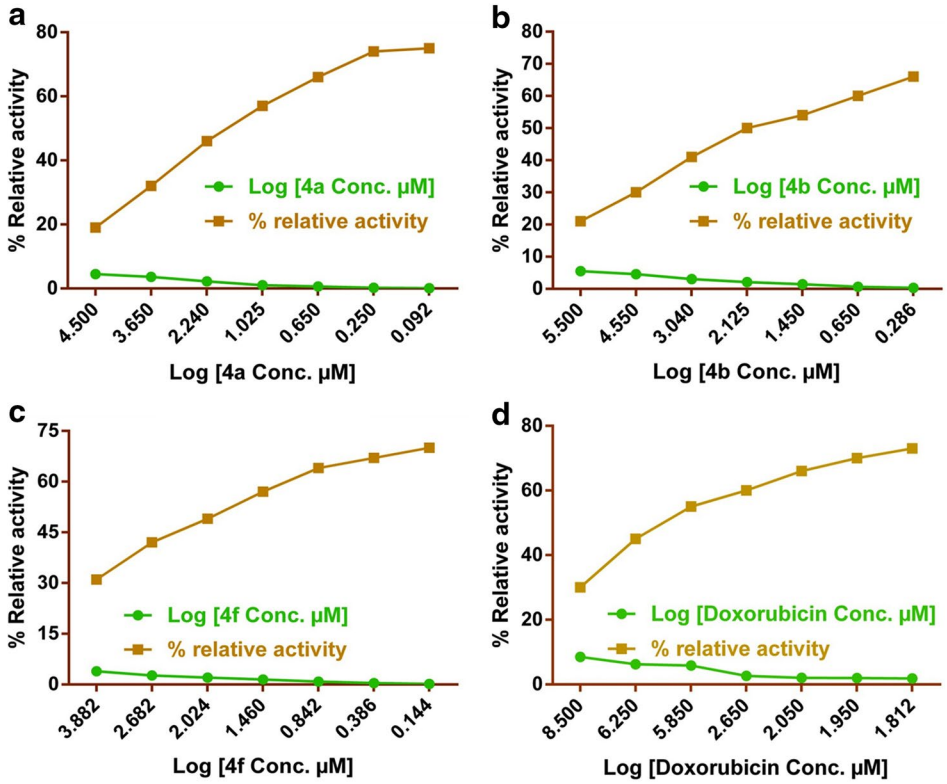


Fig. 1 **a–d** PI3K activity results of 4a, 4b, 4f, and wortmannin at various concentrations. *Note* IC_{50} values are the mean of duplicate or triplicate measurements

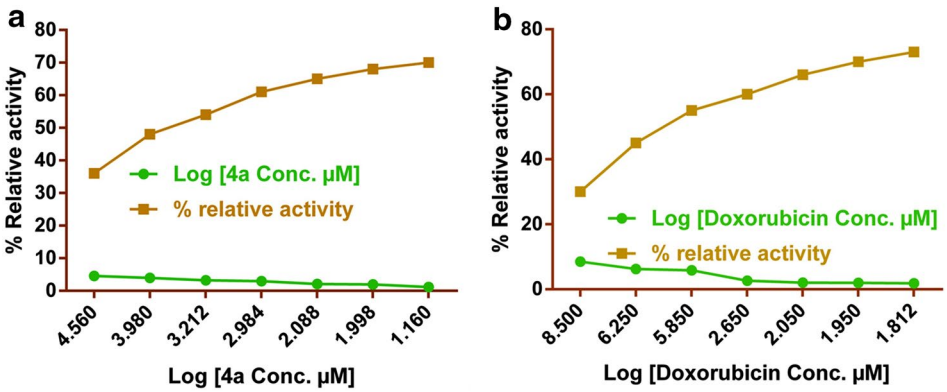


Fig. 2 **a**, **b** Anticancer activity results of doxorubicin and 4a at various concentrations

inhibition was excellent for compounds 4a, 4b, 4f–h, and 4j with a range of 59.91–74.82%. Compounds 4c, 4d, and 4k were found with <30%. Rest all PQPDs were found in the range of 52.16–58.86%. With this promising result, we tested the anticancer potential of all PQPDs except 4c, 4d, and 4k against breast cancer (MCF-7), skin cancer (G-361), and colon cancer (HCT 116) cell lines by MTT assay.

Anticancer determinations by MTT assay

The human breast cancer (MCF-7), skin cancer (G-361), and colon cancer (HCT 116) cell lines were incubated with different doses (10–150 µg/ml) of PQPDs to evaluate the anticancer activity. Cells were seeded at a density of 1×10^4 cells/well in a 96-well plate and grown for another 24 h. After 24 h of incubation, cell viability was determined by the MTT assay and the inhibitory percentage were calculated (Sup. Table 2). PQPDs 4a–l was able to inhibit the proliferation of the cancer cells. IC_{50} values indicate that some of the tested PQPDs were as active as the standard drug doxorubicin (IC_{50}1.812 µM), the standard (Fig. 2). PQPDs 4a (1.160 µM), 4b (2.07 µM), 4f (1.224 µM), 4j (1.981 µM) were found with excellent activity.

Molecular docking studies

The PQPDs (4a–l) were docked into the active sites of phosphoinositide 3-kinase (PDB ID: 2RD0). The docked

poses with lowest binding energy, hydrogen bonding, and non-covalent bonding (π–π interaction and π–cation interaction) details were recorded and validated (Table 2). The expected binding free energy for PI3K was found between −5.54 and −77.03 kcal/mol. This free energy value demonstrates the PQPDs (4a–l) having a fortunate selectivity toward PI3K inhibitory potency. 4c, 4d, and 4k have not exposed any reliable values neither lowest binding energy nor the least inhibitory constant, while 4g–i and 4l showed appreciable binding affinities and ligand efficiency.

Receptor–ligand interaction analysis between PI3K and PQPDs

The existence of H-bond and non-covalent bond interactions (π–π interaction and π–cation interactions) was measured in order to get the ligand–receptor interaction information. The π–π interactions are related to the contact between the π-orbitals of a molecular organization and the π–cation involving in the positive charge of a cation connected with the electrons in a π-system of a molecule. PQPDs (4a–l) were established π–π interactions to the Ar-2 and Ar-3 ring system of the PQPDs (4a–l) with the amino acid residues, His834 (4b, 4c, 4g, and 4i), His967 (4b and 4j), and Tyr160 (4e) of PI3K. Lys668 involved in 4h, 4j, 4k, and 4l π–cation interactions to the Ar-2, Ar-3, and Ar-4 ring system of the PQPDs (4a–l). Lys875 (4d) was another amino acid residues involving in the π–cation interactions (Sup. Figure 1–24, p19–30).

H-bonds established to Ala704 (4e); Asp837 (4g, 4h and 4l); Asp874 (4a and 4e); Gln705 (4b and 4l); Gln743 (4g and 4i); Lys875 (4d); Lys68 (4j); and Ser706 (4j). All H-bonds were found between the ligand/receptor atoms N, H, and O. H-bond angle (Å) for the ligands was from 1.814 to 2.186 Å. Expected inhibitory constant (ki) was exceptional for the compounds 4a, 4b, and 4j with 41.23, 53.33 pM, and 128.2 nM. The best interaction and least binding affinities were found for 4a (a π–π, π–cation, and H-bond), 4b (two H-bonds, three π–π interactions), 4f (two π–π, a π–cation, and H-bond), and 4j (a π–π, π–cation, and H-bond) as depicted in Fig. 3. As depicted in Table 1 and Fig. 3a–d, –CHO containing ether groups in the PQPDs 4g and 4j and –CHO containing alkanol groups in the 4a and 4b were found with best interactions, and evidently the four were found as the potent moieties among all PQPDs (4a–l). PQPDs 4c and 4l with $–CH_3$, $–O–CH_3$ (R_2) and –OH (R_1) were found with moderate interactions, while PQPDs 4e, 4h, 4k, and 4l with aryl halides and leaving groups were not contributed as active as in the inhibitory studies as well as in the anticancer evaluations a similar input reflected in the docking studies noticeably (Sup. Figure 1–24, p19–30).

Table 2 Molecular interaction of PQPDs 4a–l with PI3K (PDB ID: 2RD0)

Entity	Binding energy (kcal/mol)	Ligand efficiency	Inhibitory constant (ki)
4a	−76.25	−2.31	53.33 pM
4b	−77.03	−2.86	41.23 pM
4c	−8.56	−0.31	22.22 μM
4d	−5.54	−0.29	41.18 μM
4e	−16.16	−0.38	20.27 μM
4f	−40.87	−1.23	102.4 nM
4g	−15.88	−0.61	124.8 μM
4h	−15.69	−0.56	151.2 μM
4i	−15.78	−0.59	6.122 μM
4j	−46.97	−1.48	128.2 nM
4k	−5.62	−0.26	16.66 μM
4l	−17.14	−0.55	7.071 μM

Structure–activity relationships

In order to explore structure–activity relationship (SAR) preliminarily, PQPDs (4a–l) with different electron-withdrawing and electron-releasing groups (–Cl electron withdrawing, –F electron withdrawing, and $–CH_3$ electron donating) at R_2 position (C2), –Br (electron withdrawing), $–O–CH_3$ (electron donating), and –OH (electron donating, since it is attached to benzene ring) groups at R_1 position (C16) of quinoline ring were synthesized and evaluated for antiproliferative/anticancer activity in various cancer cell lines. In the antiproliferative activity, SAR study demonstrated a significant increase in the potency of PQPDs (4a–l) that were substituted at C2-position (R_2) with a bulky group. PQPDs 4a (IC_{50} 1.160 μM), 4b (IC_{50}2.07 μM) with –CHO containing alkanol and ether group, and 4j (IC_{50} 1.224 μM) substituted with –OMe against MCF-7 cell lines were found as the most potent moieties (Fig. 4). Among all (C2) substituted compounds, 4h (IC_{50} 2.814 μM) and 4l (IC_{50} 3.322 μM) showed moderate activity ($–CH_3$ at R_2). PQPDs 4c, 4d, and 4k, mostly substituted with the halogens –Br, –F and –Cl at R_2 along with –OH at R_1, were found as less active compounds. SAR study based on most favorable IC_{50} (of MCF-7) showed that compounds 4a, 4b, 4f, and 4j were the most potent compounds and also suggested that an appropriate degree of electron density on quinoline ring was essential to retain the activity of PQPDs (4a–l).

Discussion

Cancer is involving abnormal cell growth which is invading or spreading to various parts of the body system (WHO—World Health Organization). Discovering suitable

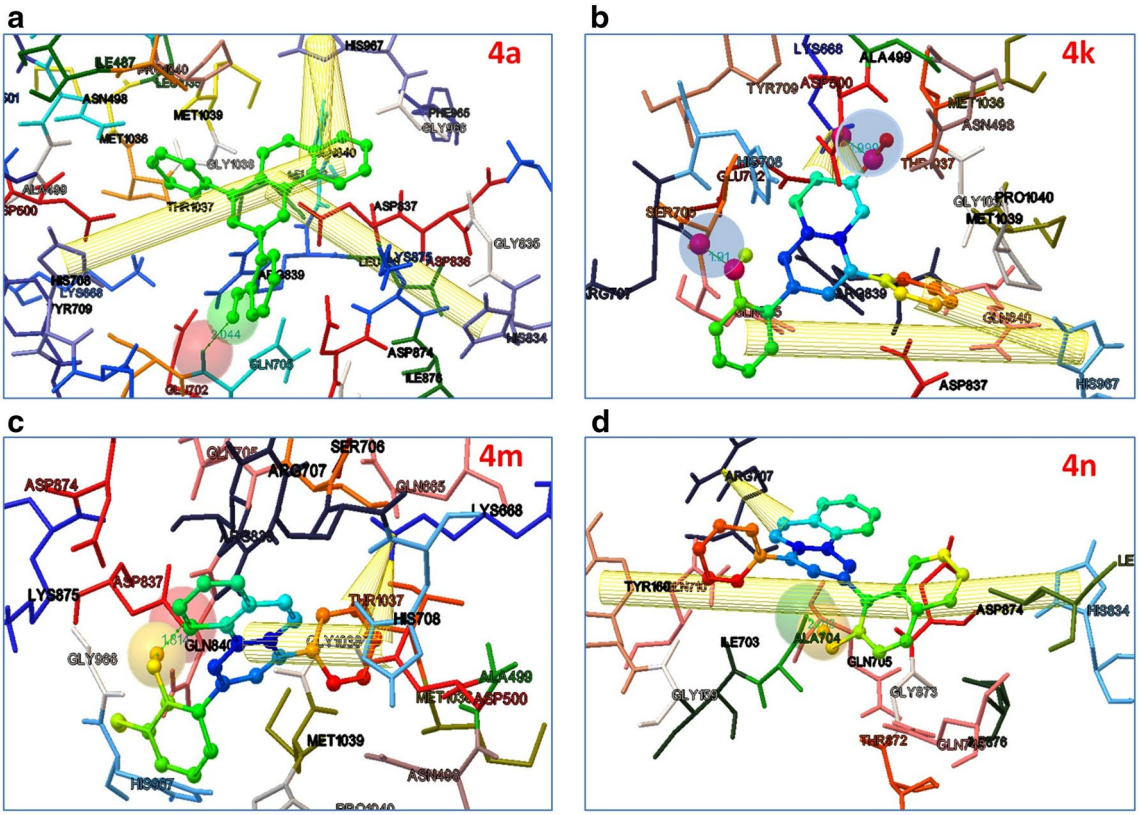


Fig. 3 **a–d** Interaction of 4a, 4b, 4f, and 4j with PI3 Kinase (PDB ID: 2RD0). *Note stick* and *balls* (PQPDs), sticks only (amino acid residues), *spherical* (H-bonds), *cylindrical* (π–π interactions), and *conical* (cation–π interactions)

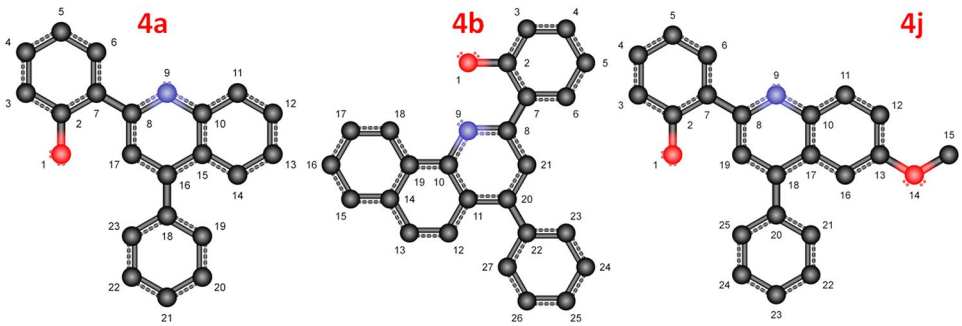


Fig. 4 PQPDs 4a, 4b, and 4j –CHO containing alkanol and –OMe groups substituted at the C2 position

chemical agents through research is vital to prevent/cure cancers. Phosphatidylinositol 3-kinases (PI3Ks) are significant molecular targets for novel anticancer agents, and they were readily recognized as the crucial regulators of apoptosis or programmed cell death [20]. PI3K pathway when abnormally activated, it is inducing carcinogenesis and tumor angiogenesis [30, 31]. Osaki et al. [32] have demonstrated the alterations of normal pathways by PI3Ks which are playing an important role in the development of cancers [32]. Kendall et al. [33] have analyzed PI3 Kinase's isoforms p110α, p110β, and p110δ for anticancer potentials and demonstrated that chemical entity inhibiting PI3K-p110α found with potential anticancer effect [33]. These are all representing the potency of inhibition ability of PI3Ks by a chemical entity which is a key part of designing, synthesis, and developing an anticancer agent. In this study, we have synthesized, evaluated, and designed the PQPDs as the potent PI3 Kinase inhibitors so as the anticancer agents.

In this study, we have synthesized, evaluated, and designed the PQPDs as the potent PI3 Kinase inhibitors so as the anticancer agents. Functional group availability of PQPDs was evaluated in support to the proposed activity. In the evaluations, –CHO and aryl halides along with

the aromatic arene, azaarene, heteroarene, and phenol ring were the substituent for PQPDs (4a–l) which were played a major role in the anticancer activity. Since PI3 Kinases playing an important role in the cancer development [34–36], PI3 Kinase enzyme inhibition assay was carried out in support to understand the therapeutic abilities of the PQPDs. 4a, 4b, and 4f were found as most potent compounds in the activity (Fig. 1). PI3K-p110α is mostly involved in the cancer development rather than other subunits.

A molecular docking study was also carried out in connection with the PI3 Kinases enzyme inhibition assay studies. The least inhibitory constant derived in the molecular docking studies coincided the PI3 Kinase inhibition assay. This indicates the association of functional groups of PQPDs in the proposed activity. Compounds 4a and 4b showed a most fortunate binding affinity values with lowest ki (inhibitory constant) 53.33 and 41.23 pM. In the past decades, quinoline scaffolds were analyzed for their anticancer potent [37]. Structure–activity relationship (SAR) studies were concerned in most of the reports to provide strong support/evidence for contribution of small molecules in the therapeutic activities. In the present study, SAR studies revealed that few compounds among PQPDs (4a–l) which were substituted with a different electron-withdrawing and electron-releasing group at R_2 position (C2) and at R_1 position (C16) of quinoline ring found as potent antiproliferative/anticancer agents. In fact, SAR studies demonstrated the resemblance between the in silico and in vitro evaluations as well as the correlation of functional group contribution in the proposed activity.

Conclusion

In conclusion, phenylquinoline phenol derivatives (PQPDs) (4a–l) were successfully evaluated as PI3 Kinase inhibitors so as the anticancer agents.

- PQPDs 4a, 4b, 4f, 4g, and 4j were displayed potent PI3 Kinase enzyme inhibition activity conducted.
- Same compounds found with similar dominance in the anticancer activity against MCF-7, a human breast cancer cell line.
- Binding mode and binding affinities in the docking evaluations favoring the PQPDs (4a–l) equipped with –CHO containing alkanol and ether groups.
- SAR study demonstrated a significant increase in the potency of PQPDs (4a–l) that were substituted at C2-position (R1) with different groups.

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Compliance with ethical standards

Conflict of interest None.

Ethical approval No animal or human subjects were used in this study. But all procedures performed in accordance with the ethical standards of the institutional and/or national research committee or comparable ethical standards.

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