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SYNTHESIS AND STUDY OF ANTICANCER ACTIVITY OF QUINOLINE DERIVATIVE USING COMPUTATIONAL CHEMISTRY

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ABSTRACT:
Quinoline has been a core molecule in the synthesis of many drugs in the field of medicinal chemistry over a decade. Innumerable Anticancer drugs with quinoline nucleus at its core have been synthesized and proved to be potential drugs. Quinoline has been a key molecule due to its versatility especially in Anti-cancer drug development by interfering through different mechanisms as cell cycle arrest, disruption of cell migration and modulation etc. The synthesis and study of a series of 6-methoxy-2-phenyl- quinoline-4-carboxylic acid derivatives using substituted Isatin derivative has been done and they have been detected as anti-cancer drugs aided by molecular docking using computational studies. The structures of the synthesized compounds have been established by 1H- NMR, 13C- NMR and IR for structural elucidation. Their anti-cancer activities were predicted by in-silico studies. Among the synthesized 6-Methoxy-2-Phenyl quinoline-4- carbohydrazide has shown better binding energy and interactions as confirmed using Molecular docking studies with PDB-ID: 6hx1.

KEYWORDS: 6-Methoxy-2-phenyl quinoline-4-carboxylic acid, 6-Methoxy-2-phenyl quinoline-4-carbohydrazide, synthesis, in-silico studies, Molecular docking, anti-cancer.

INTRODUCTION:

Cancer is one of the deadliest diseases, causing 8.2 million deaths worldwide which is expected to rise to approximately 13 million cases till 2030[i] and hence it is a great topic for research. The challenging task is to develop new entities with selectivity towards cancer cells. Developing a novel drug is a complex, risky, expensive and time-consuming venture. With decline of expenditure on research and development by pharmaceutical companies and rising costs of bringing a new molecular entity to the market the so called - "Valley of death" in anti-cancer drug development has become a highly complex problem[ii]. Fortunately, many novel technologies and methodologies have been developed to increase the efficiency of drug discovery process, and computational methodologies have become a hallmark in the anti-cancer drug discovery programs. From hit identification to lead optimization, techniques such

as ligand or structure based virtual screening are widely used in many discovery efforts. In designing potential anticancer drugs and drug candidates, computational approaches have had a major impact over the years and have given fruitful insights into the field of cancer[viii-ix].

Quinoline is a pharmacologically valuable scaffold that is prevalent in a variety of biologically active synthetic and natural compounds[iii]. The chemistry of quinoline has been a subject of intense study and different, interesting bioactivities such as antibacterial, antifungal, anti-inflammatory, antimalarial, anticancer activities[iv-vii] have been reported.

The anticancer activity of quinolines is quite broad, having been used against many cancers such as those of breast, prostrate, gastrointestinal tract, colon and liver[x-xiii]. A number of quinoline based anticancer drugs have been used clinically, including campothecin and its analogues[xv] and bosutinib[xvi-xvii]. The anticancer activity of quinoline based compounds is exerted through many mechanisms like apoptosis inhibition of angiogenesis, receptor inhibition and DNA intercalation etc[xxiii].

The hydrazine-hydrazone moiety used in conjugation with a quinoline system, has afforded compounds with antimicrobial[xviii], antimycobacterial[xix] anti-tubercular[xx-xxi] and cytotoxic activity[xxii]. Several derivatives of quinoline that act as potent anticancer agents have been synthesized[xxiv]. The Schiff's bases of quinoline-4-carboxylic acids are associated with anti-fungal, anti-bacterial activities and have wide biological activities[xxv]. Cinchophenis, a derivative of quinoline has huge medicinal value and its derivatives have been proved to be a powerful anti-microbial agent[xxvi].

Quinoline can be conjugated with different bioactive pharmacophore to obtain potent anticancer agents[xxvii]. Erugu and associates have reported the synthesis of novel quinoline-4-carboxylic acid derivatives via Pfitzinger reaction of Isatin with aromatic ketones[xxviii]. Xiang et al. have reported the efficient synthesis of substituted quinoline-4-carboxylic acid derivatives using the condensation reaction between Isatin and substituted aromatic ketone[xxix]. Gupta and co-workers have reported a high yielding synthesis of novel quinoline-4-carboxylic acid derivative via condensation of Isatin with various allylic ketones[xxx]. Chebanov et al. have discovered an efficient protocol for the synthesis of quinoline-4-carboxylic acid via facile and efficient 3 components condensation of aromatic aldehydes, some aminoazoles and pyruvic acids in DMF[xxxi]. With the literature review of some of references we arrived at the preparation of some novel quinoline derivatives as mentioned below.

EXPERIMENTAL SECTION:

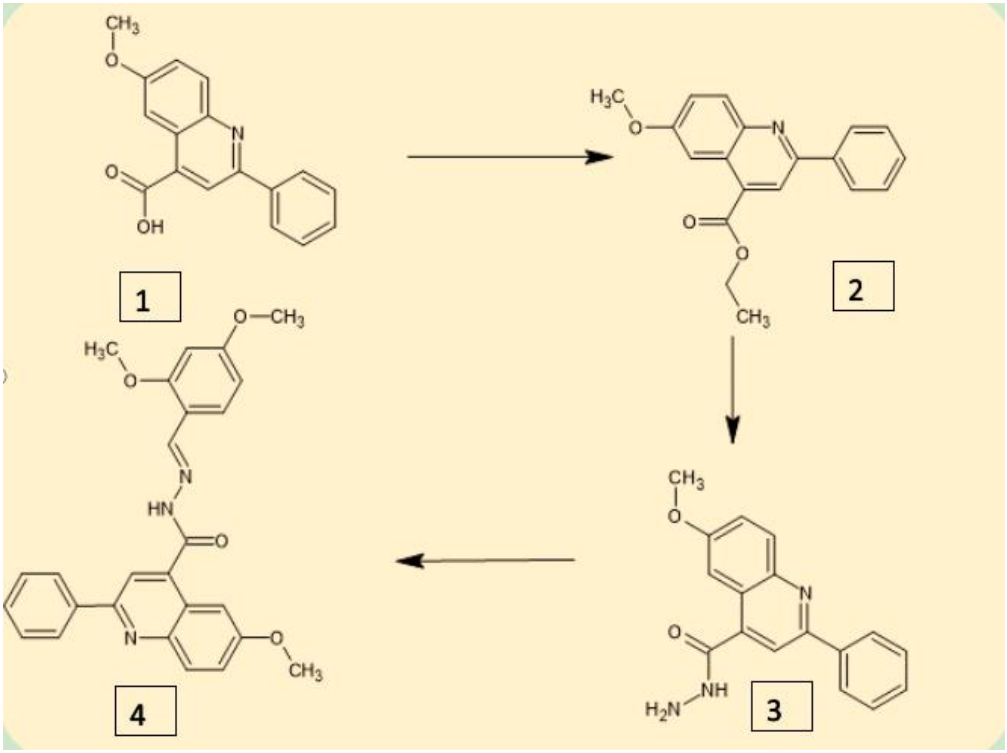


Fig 1: Reaction pathway

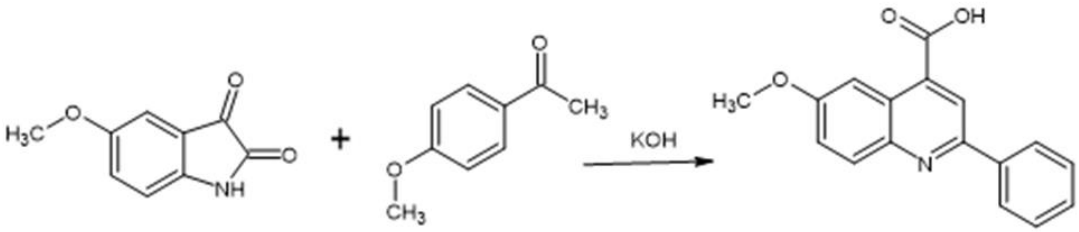
GENERAL PROCEDURE:

PROCEDURE FOR THE SYNTHESIS OF 6-METHOXY-2-PHENYLQUINOLINE-4-CARBOXYLIC ACID (1)

A mixture of 5-methoxyisatin (1.767 gms), p-methoxyacetophenone (1.80 gms) and KOH (3.36 gms) were taken in a sealed tube and dissolved in minimum amount of water. To this mixture, a minimum quantity of ethanol was added and the reaction mixture was irradiated with microwaves and the reaction temperature was 120 ^{0}C for 20 mins. The progress of the reaction was monitored using TLC using a mixture of chloroform and methanol in the ratio of 9:1.as solvents.

After the completion of the reaction, the product was extracted by dissolving it in water. The solid compound precipitated was filtered, dried and collected.

SCHEME 1



5-methoxy-isatin 4-methoxy acetophenone 6-methoxy-2-phenylquinoline-4-carboxylic acid

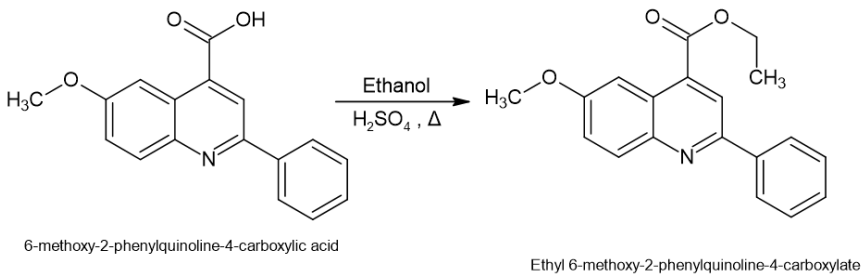
Colour **Moss green**
M.F **$C_{17}H_{13}O_3N$**
M.W **272**
Yield **75%**
M.P **230 ^{0}C**
1H-NMR (DMSO-d6, 300MHz, δ ppm): 8.61 (d, J = 7.8 Hz, 1H, quinoline), 8.40 (s, 1H, quinoline), 8.16 (d, J = 9.0 Hz, 1H, quinoline), 7.82(d, j=9.0 Hz. 1H, quinoline), 7.78-7.81 (m, 1H, aromatic), 7.77- 7.69 (m, 1H, aromatic), 7.36-7.39 (m, 2H, aromatic), 7.65-7.71 (m, 1H, aromatic); 3.40(s, 3H-OCH_3).
C-13 NMR (DMSO-d6,75.480MHz δ ppm): 167.77, 159.00, 152.94, 144.57, 135.43, 130.40, 124.62, 122.39, 119.46, 114.36, 103.80, 55.40

Table 2

Sr No.	Name of compound	Molecular Weight	Density g/cm^3	Weight taken	No. of moles
1.	5-Methoxyisatin	177.16	1.4	2.0 gms.	0.011
2.	p-Methoxy acetophenone	150.18	1.09	1.65 gms	0.011
3.	KOH	56.10	1.45	3.08 gms.	0.055

PROCEDURE FOR THE SYNTHESIS OF ETHYL- 6-METHOXY-2-PHENYLQUINOLINE-4-CARBOXYLATE (2)
5 gms of the acid (1) obtained in step-1 was taken in a R.B flask to which 10 ml of H_2SO_4 and 20 ml of Ethanol was added and refluxed for 2 hrs. After 2 hrs the ester obtained was confirmed by performing the phenolphthalein test. The progress of the reaction was monitored using TLC using Chloroform and methanol as solvents, in the ratio of 9 :1. Ester was isolated after confirmation using chloroform. The dry weight of the compound obtained after extraction was 1.5 gm.

SCHEME 2



6-methoxy-2-phenylquinoline-4-carboxylic acid

Ethyl 6-methoxy-2-phenylquinoline-4-carboxylate

Colour **Dark brown**
M.F **$C_{19}H_{18}O_3N$**
M.W **337.29**
Yield **80 %**
M.P **228 ^{0}C**

C-13 NMR (DMSO-d6, 75.480 MHz, δ ppm) : 165.83, 161.16, 158.49, 152.68, 143.14, 135.71, 129.97, 128.93, 124.45, 123.35, 119.93, 114.59, 103.63, 61.52, 55.66, 55.53, 15.21, 14.16.

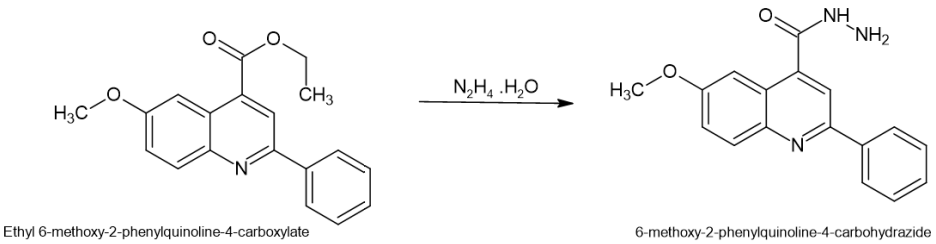
Table 3

Procedure for the synthesis of 6-methoxy-2-phenylquinoline-4-carbohydrazide (3)

Sr No.	Name of compound	Molecular Weight	Density g/cm^3	Weight taken	Number of moles
1.	6-Methoxy-2-phenylquinoline-4-carboxylic acid	309.29	-	5.0 gms.	0.016
2.	Ethanol	46.07	0.789	20 ml	0.342
3.	H_2SO_4	98	1.45	10 ml	0.147

To the product obtained (2), hydrazine-hydrate was added in minimal quantity. The reaction mixture was irradiated with microwaves at 120^{0}C for 20 mins. This yielded a peanut brown coloured solid i.e. 6-methoxy-2-phenylquinoline-4-carbohydrazide. The progress of the reaction was monitored using chloroform and methanol, in the ratio of 9:1.
After completion of reaction, the product was extracted by dissolving it in water, the solid compound precipitated. Filter, dry and collected the solid compound.

SCHEME 3



Ethyl 6-methoxy-2-phenylquinoline-4-carboxylate

6-methoxy-2-phenylquinoline-4-carbohydrazide

Colour Peanut brown
M.F $C_{17}H_{15}O_2N_3$
M.W 293.319
Yield 48.88%
M.P 240^{0}C

1H-NMR (DMSO-d6, 300MHz, δ ppm): 8.4 (s, 1H, quinoline), 8.1(d, 1H, quinoline), 8.0 (s, 1H, quinoline), 8.22 (d,2H, aromatic), 7.1 (d, 2H, aromatic), 7.36-7.39 (m, 2H, aromatic), 7.4 (m, 1H, aromatic); 3.80(s, 3H-OCH_3), 2.5(s,2H,-NH_2).

C-13 NMR (DMSO-d6,75.480MHz δ ppm) : (167.75, 160.56, 157.99, 152.95, 144.72, 135.32, 131.14, 130.52, 128.28, 124.54, 122.28, 119.32, 114.32, 103.74 55.42, 55.30).

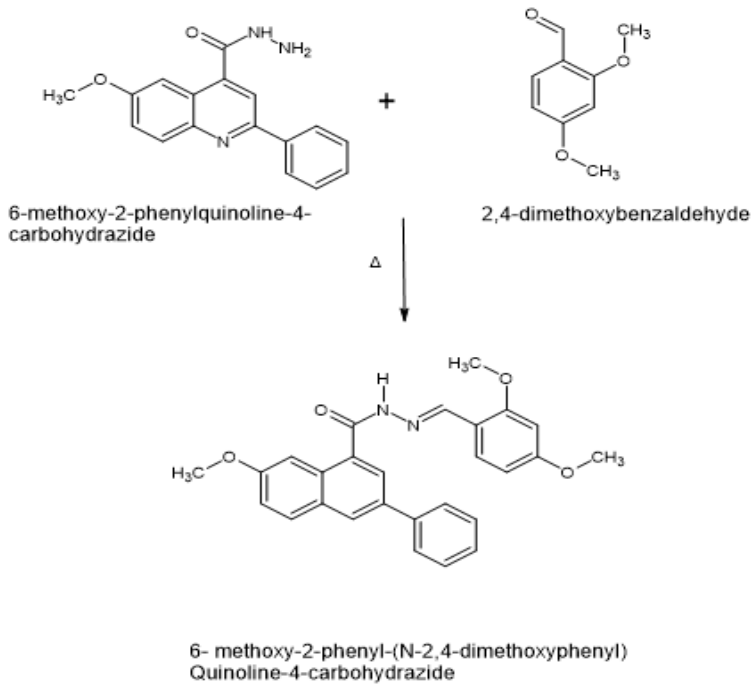
Table 4

Sr No.	Name of compound	Molecular Weight	Density g/cm^3	Weight taken	Number of moles
1.	Ethyl- 6-Methoxy-2-Phenylquinoline-4-carboxylate	309.29	-	0.9 gms.	0.0029
2.	Hydrazine hydrate	50.61	1	8 ml	0.0029

PROCEDURE FOR THE SYNTHESIS OF 2, 4-DIMETHOXY DERIVATIVE (4)

0.5g of 6-Methoxy-2-phenyl quinoline-4-carbohydrazide obtained from the above step was taken in a microwave tube and 0.2824 g of 2, 4-dimethoxy benzaldehyde was added to it. The reaction mixture was irradiated with microwaves for 20-25 mins and cooled down to room temperature. The reaction was monitored using TLC. The solvent system taken for TLC was 7:3 ethyl acetate: n-hexane.

SCHEME 4



Colour **Pale yellow solid**
M.F **$C_{26}H_{23}O_4N_3$**
Yield **55.69 %**
M.W **441.478.**
M.P **285 ^{0}C**

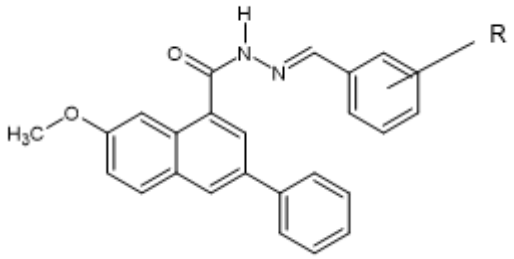
1H-NMR (DMSO-d6, 300MHz, δ ppm) :8.6(d,1 -CH) ; 8.4 (d,1H, quinoline) ; 8.27(d, 1H, quinoline) ; 8.14 (d, 2H, aromatic) ; 7.82(d, 1H, quinoline); 7.5(d, 2H, aromatic); 7.66 (m, 1H, quinoline); 7.12 (m, 1H, aromatic); 7.09(d,1H, aromatic) ; 6.93 (d, 1H, aromatic); 3.80(s, 3H-OCH_3 quinoline); 3.49(s, 6H -OCH_3, aromatic).

C-13 NMR (DMSO-d6, 75.480 MHz δ ppm): 167.76, 160.53, 157.97, 152.93, 144.72, 135.30, 131.13, 130.52, 128.26, 124.53, 122.25, 119.30, 114.29, 103.73, 55.39, 55.27.

Table 5

Sr No.	Name of compound	Molecular Weight	Density g/cm^3	Weight taken	Number of moles
1.	6-Methoxy-2-Phenylquinoline-4-carbohydrazide	293.31	-	0.5 gms.	0.00170
2.	2,4-Dimethoxy benzaldehyde	166.17	1.114	0.2824 gms	0.00170

SCHEME 5



R = 2,4-$MeOC_6H_3CH$-, m- $NO_2C_6H_4CH$-, 2,4- OHC_6H_3CH-, $PhMeCH$-, Ph_2CH-, $MeCH$-, Me_2C-, Ph_2C-, $PhSO_2$, etc.

MATERIAL AND METHOD:

All reagents used in the preparation of Quinoline derivatives were purchased from SRL**.** Solvents and chemicals used in the reactions were of AR grade. The progress of the reaction and purity of the sample were checked by TLC using chloroform and methanol in the ratio of 9:1. For TLC stationary phase used was silica gel coated aluminium sheets (Silica gel 60 F254) procured from Merck India. ^{1}H NMR was recorded using Avance Neo NB 300 MHz NMR Instrument by using TMS as internal standard and the chemical shift values are expressed in δ (ppm scale). Melting point of the compounds synthesized were recorded by open capillary method by using melting point model check melt - VR of Spectra Lab Instruments Pvt Ltd. FT-IR spectra (ν in cm-1) using KBr discs were recorded on Perkin-Elmer FT-IR spectrophotometer

IN SILICO STUDIES :

PREPARATION OF RECEPTORS AND LIGANDS FOR DOCKING.

The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allows one to characterize the behavior of small molecules in the binding site of target proteins and to elucidate the fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation, its position and orientation within these sites (usually referred to as pose) and assessment of the binding affinity. These two steps are related to sampling methods and scoring schemes, respectively[xiv].

Chemical structure of the ligand molecule was sketched using the software 'ACD/CHEMSKETCH' and converted into (.mol2) for 3D optimization using AVOGADRO (with energy minimization) or OPEN BABEL. The crystal structure of a kinase inhibitor (PDB ID 6hx1) was downloaded from RCSB Protein Data Bank in (.pdb) format. With both the protein and ligand in the desired format, the next step is the docking which includes the addition of hydrogen atoms and Kolmann charges, energy minimization, and removal of water molecules. For these steps, we used molecular modelling simulation software - 'AUTO DOCK TOOLS'. The HIT ligand compounds were docked on the protein selected. The selected ligand is saved in(.pdbqt) format. For the macromolecule, specific parameters and the grid box are set according to the requirements of the docking process. The grid parameter file is saved in (.gpf) format. Then AUTOGRID is run to create the (.glg) file. The next step is docking, (set from 50 to 100 runs) to obtain the best poses after docking. The docking is based on LAMARCKIAN GA, which selects the best pose and docking that runs on the principle of - 'only the fittest survive'. The (.dpf) file was saved. Later on, the AUTODOCK was run and launched for generating the (.dlg) file. The (.dlg) file was checked for the RMSD table and the binding energies of different poses of the ligand docked were evaluated. The poses with the least energies (the most stable ones) were saved as a (.pdb) file for analysis.

For Analysis, the visualization tool `PyMOL' was used. The desired poses of the ligand and protein and were evaluated for the interactions and best fit in the pocket.

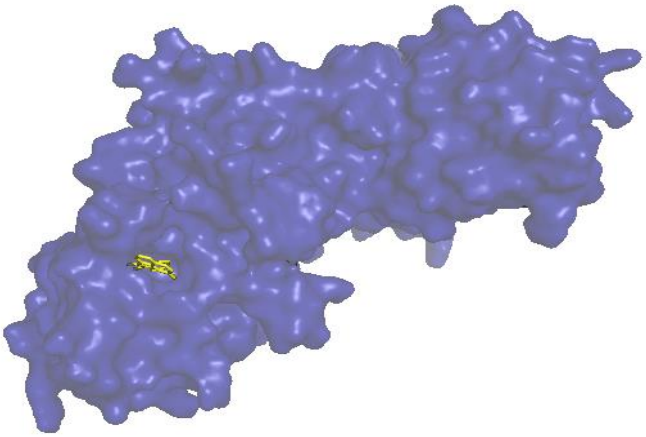


Fig 2: Quinoline derivative effectively binding with 6hx1 protein

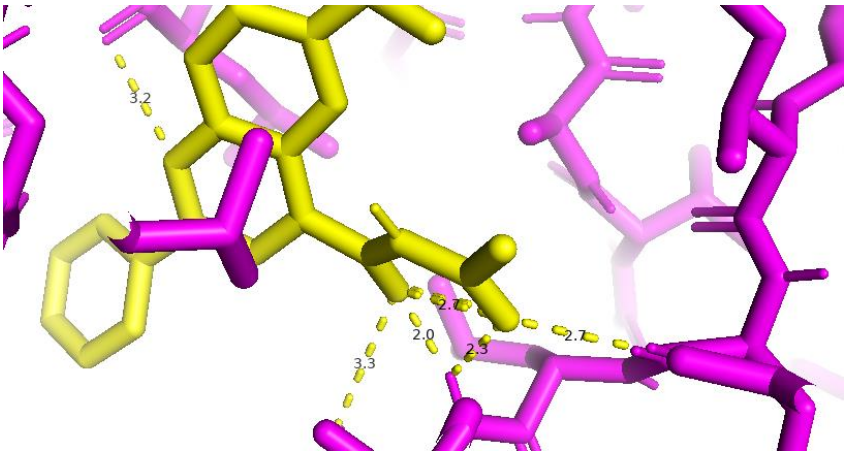


Fig 3: Polar interactions between drug derivative and protein

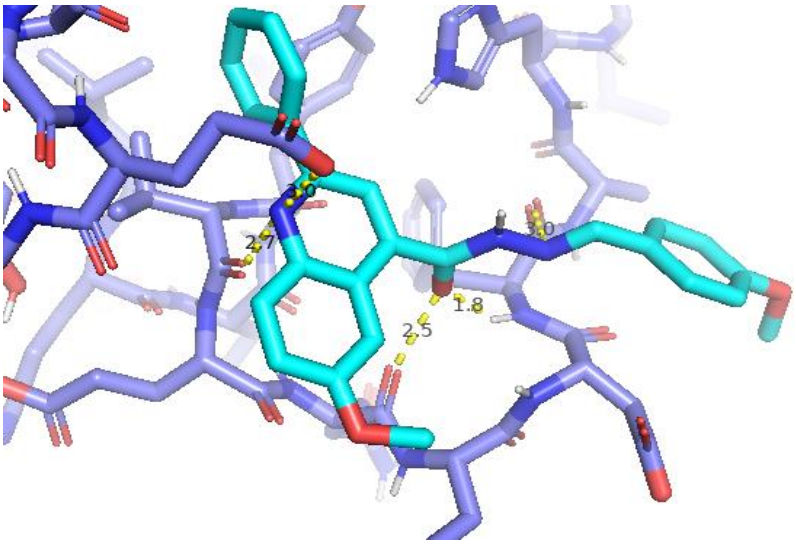


Fig 4: Polar interactions

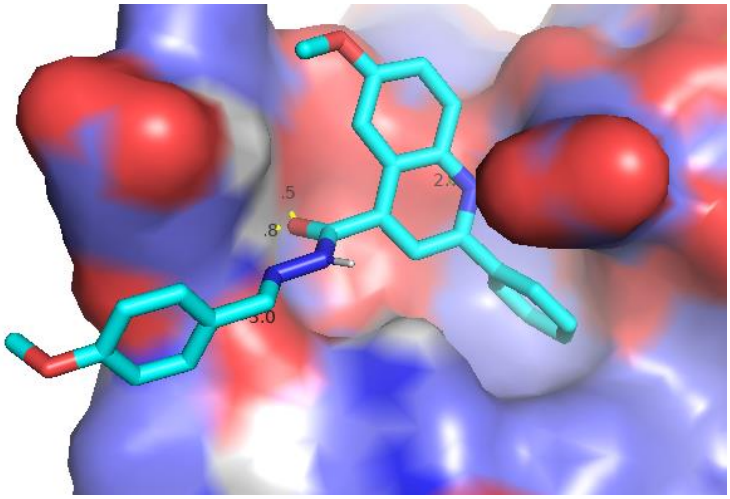


Fig 5: Drug derivative inside the pocket

RESULTS AND DISCUSSION:

6-Methoxy -2-phenyl quinoline -4- carboxylic acid was synthesized using a procedure mentioned in the experimental section. The Quinoline-4- carboxylic acid were further converted to the corresponding ethyl ester. The ester was treated with hydrazine to form 6-methoxy -2-phenyl quinoline -4- carbohydrazide . A new series of 6-methoxy -2-phenyl quinoline -4- carboxylic acid hyrdrazides were synthesized using the lead compound. All the target compounds were evaluated in-silico and were found to be good bioactive agents.

Table 1: Ligand parameters

Sr. no.	Ligand	B.E* (kcal/mol)	No. of polar interactions (1.5 - 3.0 Å)	GI*	BBB*	Lipin-ski	Lead-likeness	Solubility	Synthetic access-ibility	LogP
1.	6-Methoxy-2-Phenylquinoline-4-carboxylic acid	-5.98	2	High	Yes	Yes	Yes	Moderate	2.18	2.8
2.	Ethyl-6-methoxy-2-phenyl quinoline-4-carboxylate	-5.97	3	High	Yes	Yes	No (1 violation)	Poor	2.73	4.89
3.	6-Methoxy-2-phenyl quinoline-4-carbohydrazide	-8.07	5	High	Yes	Yes	No (1 violation)	Moderate to poor	2.13	3.52
4.	2,4-Dimethoxy benzaldehyde derivative	-8.03	5	High	No	Yes	No (3 violation)	Moderate to poor	3.49	4.25
5.	2,4-Dihydroxy derivative	-8.31	5	High	Yes	Yes	No (3 violation)	Moderate to poor	3.08	3.9
6.	4-Methoxy derivative	-6.68	5	High	Yes	Yes	No (2 violation)	Moderate to poor	3.04	4.18
7.	Benzyloxy benzaldehyde derivative	-6.52	6	High	No	Yes	No (3 violation)	Poor to insoluble	3.54	5.39
8.	6-Methoxy-2-Phenylquinoline-4-carboxamide	-8.88	5	High	Yes	Yes	Yes	Good	2.17	2.63

***Note:**
B.E - Binding energy
GI - Gastrointestinal tract
BBB - Blood brain barrier

CONCLUSIONS:

A novel series of quinoline derivatives were synthesized using microwave method and were characterized and evaluated for their anti-cancer activities using in-silico techniques. All compounds showed good interaction with the active site amino acid of carbonic anhydrase-I and protein kinase A. IRE1 Alpha kinase inhibitor (PDB ID: 6HX1) was selected as a suitable target and molecular docking of the hit and lead compounds was done. Of all the lead compounds, 6-methoxy-2-phenylquinoline-4-carboxamide was found to be the best molecule with a binding energy of -8.8 $kJ.mol^{-1.}$. Among all the compounds synthesized (1-4), 2,4-

Dimethoxy benzaldehyde derivative (4) was the most promising molecule with a binding energy of -8.03 $kJ.mol^{-1}$.

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