Synthesis and Molecilar Docking study of 2-Aryl/Heteroaryl quinoline - 4-Carboxylic Acids for Antimalerial, Antituberculosos and Anticance Activities

P.S. PRADEEP[1], T.O. SHRUNGESH KUMAR[1], N. PRASHANTHA[2], K.M. MAHADEVAN[*1]

[1]Department of Post Graduate Studies and Research in Chemistry, School of Chemical Sciences, Kuvempu University, P. G. Centre, Kadur, Karnataka-577 548, India.
[2]Department of Medicinal Chemistry, Scientific Bio-Minds, Bangalore-560 092, Karnataka, India.
E-mail: mahadevan.kmm@gmail.com

Abstract

Various 2-aryl/heteroaryl-quinoline-4-carboxylic acid derivatives (3a-j) were obtained by Pfitzinger synthesis and were attempted for antimalarial, antituberculosis and anticancer properties through molecular docking studies. All newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and LCMS analysis. The preliminary in-silico studies such as ADMET indicates the potential drug likeliness of the compounds 3a-j. For instance, absorption is between 82-91%, BBB penetration is in expected range. The TPSA values are lies between 50.191 and 77.893 $Å^2$ which indicates good oral bioavailability. The toxicity profile of the compounds 3a-h found safe for mutagenicity, tumorigenicity, irritative and reproductive effect. However all compounds shows more than 95 % in the plasma binding.

Excellent docking score was obtained against malarial protein (PDB ID 1CET) for all compounds. Particularly the compound 3d and 3b forms five hydrogen bonds with the interaction energy -8.29 kcal/mol and 8.03 kcal/mol respectively. Against tuberculosis protein (PDB ID 2X22), 3b and 3g has shown good interaction by forming three and five hydrogen bonds respectively with the interaction energy of -7.90 kcal/mol and -8.36 kcal/mol. In the case of cancer protein (PDB ID 1S63), the compounds 3b and 3e have shown good interaction by forming three and four hydrogen bonds with the binding energy of -7.82 kcal/mol, and -8.57 kcal/mol respectively. Thus most of the quinolines 3a-j, shown fair drugs score, bioavailability, and low potential risk. In particular the compound 3b has shown promising binding result and excellent ADMET score to become potential drug.

Keywords: Pfitzinger synthesis, 2-aryl/heteroaryl-quinoline-4-carboxylic acids, Molecular docking, Antimalarial, Antituberculosis, Anticancer.

Introduction

Quinolines are found with ubiquitous structural motifs in many natural products and biologically active pharmaceuticals. Structural feature containing Quinoline moiety have possess high importance in the various natural products and pharmaceutical agents and exhibits broad range of biological activities such as antimalarials, [1] antibacterials, [2] antifungals [3] and anticancer agents. [4] Antinuclear inhibitors of immunodeficiency virus [5] Etc. Frequently in the literature, studies concerning novel 2-heteroarylquinoline derivatives were reported [6] and among the quinoline derivatives, Quinoline-4-

carboxylic acids are found most significant series having wide medicinal effects and industrial applications. Historically quinolines are found among most of the important antimalarial drugs ever used, for example, Chloroquine, Mefloquine, Quinacrine, Mepacrine, Amodiaquine, Piperaquine, Tafenoquine, Primaquine and Pyrimethamine [7]. Various Quinoline carboxylic acid and their analogues have shown wide variety of medicinal properties including antitumor, [8] antiviral [9, 10] and estrogenic activity [11]. Quinoline compounds containing various heterocyclic substitution at 2- position have shown wide verities of pharmaceutical activity such as Anticancer, anti-inflammatory and antifungal behavior [12]. Recently Meléndez Gómez et al., reported inhibition of C. albicans prolyl-tRNA synthetase with -(furan-2-yl)quinoline-4-carboxylic acid (Figure 1) and dermatophytes displayed through potent *in vitro* antifungal activity [13, 14].

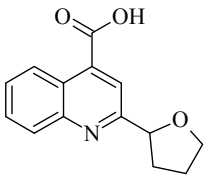


Figure 1

Due to wide varieties of medical applications including anti-tumor and anti-viral activity of Quinoline-4-carboxylic acids made to develop various synthetic routes. Among the many classical methods for the synthesis of quinolines [15], the Pfitzinger synthesis had been the best route to obtain quinoline-4-carboxylic acids, which involves the reaction of isatin with ketones containing the $–CH_2CO–$ group in the presence of sodium hydroxide or potassium hydroxide. Latter this reaction known as Pfitzinger reaction [16] and it's a powerful and efficient method to synthesis these types of compounds. Quinoline-4-carboxylic acid was the key processor to synthesize various quinoline derivatives for wider applications. Recently Vatsala *et al*., reported the mechanism of base induced ring opening of isatin derivatives to the isatoic acid by condensation with ketones [17]. Hence, encouraged by the biological activities exhibited by quinoline carboxylic acids and in continuation of our effort to identify new quinoline based therapeutic agents [18-26], in the present investigation we report one pot Pfitzinger synthesis of structurally distinct novel 2-aryl/heteroaryl-quinoline-4-carboxylic acids **(3a-j)** by using isatin and various substituted acetyl heterocyclic compounds.

Experimental

The TLC was performed on alumina silica gel 60 F254 (Merck). The mobile phase was hexane and ethyl acetate (7:3 v/v) and detection was made using UV light (254 nm). Melting points of the synthesized compounds were determined by electrothermal apparatus in open capillaries and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra recorded on Brucker (Bangalore, India) AM 400 (at 400 MHz and 100 MHz, respectively) model spectrophotometer in $CDCl_3$ or DMSO-d_6 as solvent. Chemical

shifts are expressed as δ values relative to TMS as internal standard. Mass spectra were recorded on a Jeol SX 102=DA-6000(10 kV) FAB mass spectrometer.

General procedure for the synthesis of 2**-aryl/heteroaryl-quinoline-4-carboxylic acids (3a-j)**

The mixture of commercially available isatin (**1),** acetyl aromatic compound (**2a-j),** 33% aqueous potassium hydroxide solution in EtOH solvent was refluxed. After 14 h to 16 h the crude product was cooled to ambient temperature and poured into crushed ice and acidified to pH 1 using 1M HCl. The precipitate was collected by filtration washed with water and dried under vacuum to obtain crude product. The crude product obtained was purified by column chromatography with silica gel (60-120 mesh, petroleum ether: ethyl acetate, 7:3 v/v) to get 2-aryl/heteroaryl-quinoline-4-carboxylic acids (3a-j). The structures of all the derivatives were confirmed by spectral analysis like ^{1}H NMR, ^{13}C NMR and LCMS.

2-(furan-2-yl)quinoline-4-carboxylic acid (3a)

^{1}H NMR (400 MHz, DMSO-d_6): δ=14.16 (s, 1H), 8.88 (d, *J*=2.40 Hz, 1H), 8.29 (s, 1H), 8.03 (d, *J*=5.40 Hz, 1H), 7.45 (d, *J*=3.20 Hz,1H), 7.07 (t, *J*=2.40 Hz, 1H), 7.05 (t, *J*=1.20 Hz,1H), 6.75-6.76 (m, 1H), 6.35-6.36 (m, 1H)ppm.^{13}C NMR (100 MHz, DMSO-d_6) *δ*=108.33, 112.53, 113.04, 113.47, 117.68, 120.58, 125.08, 127.06, 135.95, 141.59, 144.17, 145.90, 159.43, 166.6 ppm. MS. *m/z* =340.17 (M^+1).

2-(5-methylfuran-2-yl)quinoline-4-carboxylic acid (3b)

^{1}H NMR(400 MHz, DMSO-d_6): δ=14.00 (s, 1H), 8.83 (d, *J*=2.40 Hz, 1H), 8.26 (s, 1H), 8.01 (d, *J*=5.20 Hz, 1H), 7.06 (t, *J*=2.00 Hz, 1H), 7.00 (t, *J*=1.60 Hz, 1H), 6.18 (d, *J*=2.40 Hz, 1H), 6.17 (d, *J*=2.40 Hz, 1H), 4.13 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ*=14.2, 108.11, 113.98, 121.77, 122.85, 124.21, 129.45, 130.06, 130.28, 131.06, 135.23, 146.42, 151.73, 159.23, 166.95 ppm. MS. *m/z* =353.09 (M^+).

2-(1,5-dimethyl-1H-pyrrol-2-yl)quinoline-4-carboxylic acid (3c)

^{1}H NMR(400 MHz, DMSO-d_6): δ=14.10 (s, 1H), 8.63 (d, *J*=8.00 Hz, 1H), 8.28 (s, 1H), 8.07 (d, *J*=7.60 Hz, 1H), 7.82 (t, *J*=1.60 Hz, 1H), 7.67 (t, *J*=1.20 Hz, 1H), 7.44 (d, *J*=3.20 Hz, 1H), 6.74-6.75 (m, 1H), 3.53 (s, 3H), 2.45 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ*=16.64, 29.30, 110.54, 115.36, 121.34, 122.78, 124.68, 128.32, 130.13, 131.87, 131.93, 135.43, 146.58, 151.85, 158.32, 167.03ppm. MS. *m/z* =266.11 (M^+).

2-(4-bromophenyl)quinoline-4-carboxylic acid (3d)

^{1}H NMR(400 MHz, DMSO-d_6): δ=14.00 (s, 1H), 8.64 (d, *J*=8.40 Hz, 1H), 8.46 (s, 1H), 8.26 (d, *J*=5.20 Hz, 2H), 8.16 (d, *J*=8.40 Hz, 1H), 7.87 (t, *J*=5.20 Hz, 1H), 7.77 (d, *J*=1.60 Hz, 2H), 7.70 (t, *J*=1.20 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ*=118.87, 123.50, 123.57, 125.37, 127.96, 129.22, 129.67, 130.33, 131.89, 136.94, 137.84, 148.22, 154.60, 167.44ppm. MS. *m/z* =328.06 (M^+).

2-[(E)-2-phenylethenyl]quinoline-4-carboxylic acid (3e)

^{1}H NMR (400 MHz, DMSO-d_6): δ=14.58 (s, 1H), 8.52 (d, *J*=8.40 Hz, 1H), 8.48 (s, 1H), 8.28 (d, *J*=5.20 Hz, 1H), 8.17 (d, *J*=9.20 Hz, 1H), 7.81 (d, *J*=2.40 Hz, 1H), 7.75-7.77 (m, 3H), 7.55 (d, *J*=16.40 Hz, 1H), 7.43 (t, *J*=7.60 Hz, 2H), 7.34-7.35 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ*=118.83, 120.61, 123.50, 125.38, 127, 96, 128.84, 129.21, 130.05, 131.13, 131.47, 134.75, 136.05, 136.85, 137.01, 148.29, 154.62, 155.32, 167.56 ppm. MS. *m/z* =276.15 (M^+).

2-[(E)-2-(4-chlorophenyl)ethenyl]quinoline-4-carboxylic acid (3f)

^{1}H NMR (400 MHz, DMSO-d_6): δ=14.27 (s, 1H), 8.46 (d, *J*=8.40 Hz, 1H), 8.26 (s, 1H), 8.13 (d, *J*=5.20 Hz, 1H), 8.07 (d, *J*=9.20 Hz, 1H), 7.87 (d, *J*=2.40 Hz, 1H), 7.65-7.66 (m, 1H), 7.35-7.36 (m, 2H), 7.23-7.26 (m, 2H), 7.20-7.21 (m,1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ*=118.78, 119.93, 123.54, 125.21, 126, 43, 127.24, 128.93, 129.85, 130.33, 131.78, 135.12, 136.03, 136.73, 135.65, 148.38, 150.83, 156.45, 167.98 ppm. MS. *m/z* =309.95 (M^+).

2-(2,4,5-trimethoxyphenyl)quinoline-4-carboxylic acid (3g)

^{1}H NMR(400 MHz, DMSO-d_6): δ=14.78 (s, 1H), 8.66 (d, *J*=8.40 Hz, 1H), 8.42 (s, 1H), 8.10 (d, *J*=8.40 Hz, 1H), 7.79 (t, *J*=6.80 Hz, 1H), 7.65 (t, *J*=8.40 Hz, 1H), 7.57 (s, 1H), 6.86 (s, 1H), 3.85-3.86 (m, 6H), 3.70 (s, 3H)ppm.^{13}C NMR (100 MHz, DMSO-d_6) *δ*=13.23, 55.77, 56.10, 118.20, 123.32, 124.21, 125.48, 128.87, 123.73, 124.22, 125.24, 129.87, 131.48, 133.74, 143.15, 146.86, 151.50, 155.84, 167.25ppm. MS. *m/z* =340.11 (M^+1).

2-(naphthalen-2-yl)quinoline-4-carboxylic acid (3h)

^{1}H NMR(400 MHz, DMSO-d_6): δ=14.02 (s, 1H), 8.88 (d, *J*=1.20 Hz, 1H), 8.67 (d, *J*=8.40 Hz, 1H), 8.50 (d, *J*=1.60 Hz, 1H), 8.23-8.23 (m, 2H), 8.16-8.17 (m, 2H), 8.10 (d, *J*=8.80 Hz, 1H), 7.98-7.99 (m, 1H), 7.88 (t, *J*=1.60 Hz, 1H), 7.73 (t, *J* = 1.60 Hz, 1H), 7.58-7.59 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ*=119.32, 123.45, 124.39, 125.40, 126.58, 127.01, 127.17, 127.53, 127.78, 128.46, 128.86, 129.73, 130.03, 133.59, 135.17, 137.64, 148.39, 155.60, 167.60ppm. MS. *m/z* =300.15 (M^+1).

2-(1-hydroxynaphthalen-2-yl)quinoline-4-carboxylic acid (3i)

^{1}H NMR(400 MHz, DMSO-d_6): δ=14.11 (s, 1H), 10.07 (s, 1H), 8.77 (d, *J* = 8.00 Hz, 1H), 8.77 (d, *J* = 8.00 Hz, 1H), 8.13 (d, *J* = 7.60 Hz, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.80 Hz, 1H), 7.86-7.87 (m, 1H), 7.77 (t, *J* = 1.60 Hz, 1H), 7.46 (t, *J* = 2.00 Hz, 1H), 7.29-7.30 (m, 3H)ppm. ^{13}C NMR (100 MHz, DMSO-d_6) *δ*=118.35, 119.20, 122.83, 123.16, 123.67, 125.42, 125.54, 126.71, 127.82, 127.86, 128.03, 129.44, 129.78, 130.40, 132.72, 135.92, 148.29, 152.83, 156.60, 167.51ppm. MS. *m/z* =316.12 (M^+1).

2-(anthracen-9-yl)quinoline-4-carboxylic acid (3j)

^{13}C NMR (100 MHz, DMSO-d_6) *δ*=118.98, 118.91, 118.31, 118.32, 119.03, 120.52, 120.31, 122.43, 123.24, 125.01, 126.32, 127.01, 127.56, 127,83, 128.64, 129.22, 130.23, 132.57, 135.96, 142.97, 148.23, 152.54, 159.48, 167.04 ppm. MS. *m/z* =350.14 (M^+1).

In-silico studies on pharmacological properties

Pharmaceutical properties and ADME (Absorption, distribution, Metabolism and excretion) are influenced to encode the balance among the molecular properties of the compounds to predict drug likeness [27]. As per Lipinski rule, if violation found more than one rule there may be problems found in oral bioavailability [28]. Based on the parameters like TPSA, Volume, Number of rotatable bonds and molecular descriptors as per Lipinski's rule of five the drug likeness of the synthesized compounds were estimated where as bioavailability and membrane permeability are linked with Partition co-efficient (Log P), Hydrogen bonds acceptors and donors, Molecular weight and finally number of rotatable bonds is very important to understand the flexibility, conformational changes and receptors or channels for binding. [29]

Molecular properties of the compounds were evaluated with the help of Molispiration (www.molinspiration.com) [30] and the drug-likeness, drug score, aqueous solubility and also explored the potential risk of Toxicity like mutagenic, tumorigenic, irritant, reproductive risks of synthesized compounds virtually by using the OSIRIS property explorer software (http://www.organic-chemistry.org/prog/peo/)[31].

Topological polar surface area (TPSA) is the summation of surface contributions of polar fragments and a good indicator for the drug absorption in the human intestine (TPSA<140 $Å^2$) and for the penetration in Blood brain barrier (TPSA< 60 $Å^2$) [32] and the same used to calculate the percentage of Absorption (%ABS). According to Zhao et al. the percentage of absorption was estimated using the Equation: % ABS = 109 − (0.345 × TPSA) [33]

The *in-silico* ADME properties were predicted by using Accelrys Discovery studio 2.1 in which various pharmacokinetic parameters like Human Intestinal Absorption, blood-brain-barrier (BBB) penetration, Plasma protein binding (PPB), cytochrome CYP2D6 inhibition, Aq. solubility, and hepatotoxicity levels were predicted. The mathematical models to predict the properties quantitatively by the set of rules or keys were inbuilt in the module and the same has been cross checked [34-35] (Table 1, 5).

Table 1: Standard level information of ADME descriptors. (Discovery studio 2.5).

Aqueous Solubility & Drug Likeness		Blood Brain Barrier penetration		Human Intestinal Absorption		CYP2D6	
Level	Intensity	Level	Intensity	Level	Intensity	Level	Intensity
0	Extremely low	0	Very high	0	Good	0	Non inhibitor
1	No, but possible	1	High	1	Moderate	1	inhibitor
2	Yes, low	2	Medium	2	Poor		
3	Yes, good	3	Low	3	Very Poor	Hepatotoxicity	
4	Yes, optimal	4	Undefined			Level	Intensity
5	No, too soluble					0	Nontoxic
6	unknown					1	Toxic

Molecular docking studies

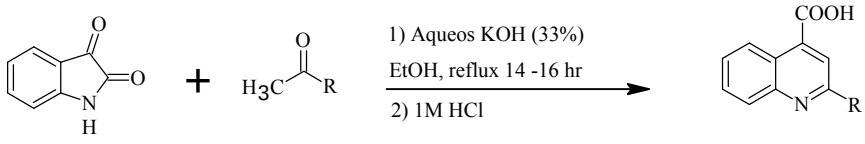
Molecular docking studies of synthesized compounds **3a-j** along with the protein receptors was carried out by using AutoDock from the Scripps Research Institute. The AutoDock helps to add hydrogen to polar hydrogens those are bonded to electronegative atoms like nitrogen and oxygen. Detection of Gasteiger charges within active sites of amino acids was computed and the charges are spread across total residue of polar and non-polar hydrogen bonds. By selecting a flexible and rigid molecule to create grid

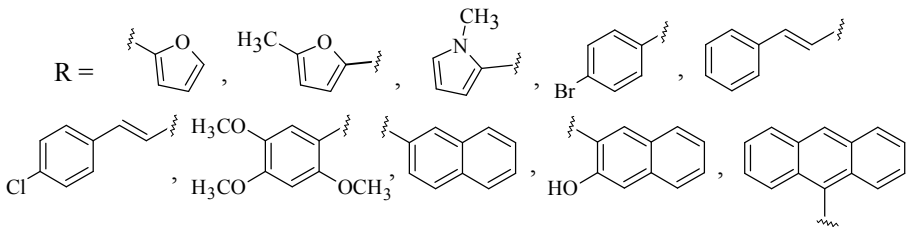
map of size 80x80x80 from x, y and z-axis and the resultant compounds were used to compute molecular stimulation parameters by Lamarckian genetic algorithm [36]. Each simulation was carried about 10 times which ultimately yielded 10 docked conformations. From this, the least energy conformation was regarded as the best binding conformation. The results were analyzed based on clusters of RMSD, and hydrogen bonding interactions. At the end, the reverse validation processes ensured the identified hits that fitted with generated pharmacological models and active sites of target proteins. Since all the parameters were required for molecular docking, the pharmacophore mapping were consequently fixed and used in regular process. The 3D crystal structures of target protein were directly downloaded from Protein data bank (PDB). The *Plasmodium falciparum lactate dehydrogenase* (PDBID: 1CET), the enoyl-ACP reductase in *Mycobacterium tuberculosis* (PDBID: 2X22) and *Human protein farnesyltransferase* (PDB ID: 1S63) were selected as these are an attractive targets for the development of novel drugs against malarial, tuberculosis and cancer. The conformational protein structure is modeled and visualized using Swiss PDB Viewer.

Results and discussion

Chemistry

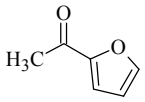
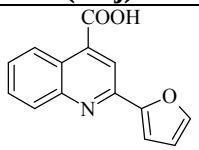
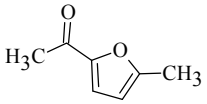
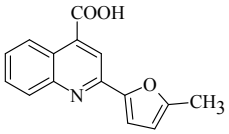
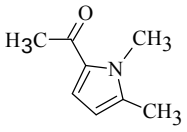
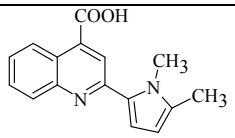
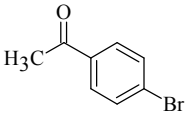
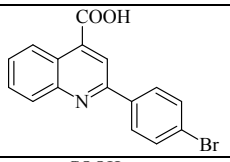
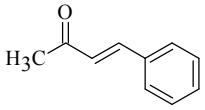
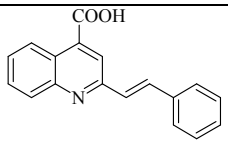
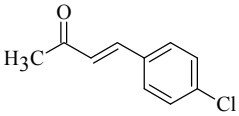
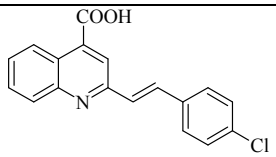
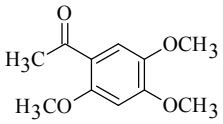
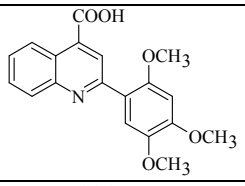
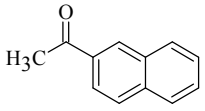
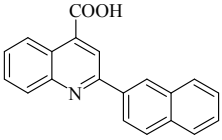
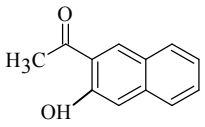
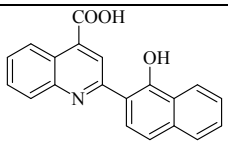
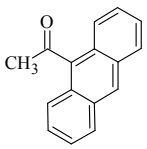
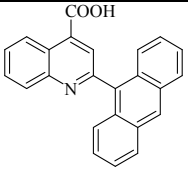
The syntheses of 2-phenyl-quinoline-4-carboxylic acids **(3a–j)** are depicted in **Scheme-1**. The model reaction was carried out by Pfitzinger reaction [39], the mixture of commercially available isatin (**1)** and 1-(furan-2-yl)ethanone (**2a)** were boiled in 33% aqueous potassium hydroxide solution with EtOH solvent. After, 14 h the crude product isolated and was purified by column chromatography with silica gel (60-120 mesh, petroleum ether: ethyl acetate, 7:3 v/v). To our delight we obtained the product as expected that is 2-(furan-2-yl)quinoline-4-carboxylic acid **(3a)**. The structure **3a** was confirmed by spectral analysis like ^{1}H NMR, ^{13}C NMR and LCMS. Similar procedure was followed to synthesize remaining derivatives (table 2), and were confirmed by ^{1}H NMR, ^{13}C NMR and LCMS, the physical data and corresponding yields were tabulated in **Table-2**. Further, the structures of all synthesized compounds were subjected to *in silico* studies.





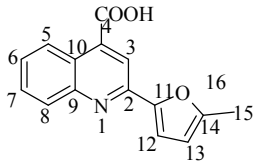
Scheme 1 Pfitzinger synthesis of 2-aryl/heteroaryl-quinoline-4-carboxylic acids **(3a–j)**

Table 2: Physical data of 2-aryl/heteroaryl-quinoline-4-carboxylic acids (**3a-j**).

Entry	Aromatic acetyls	Product (3a-j)	Yield (%)	MP^{0}C
3a			80	250-255
3b			78	245-250
3c			75	225-230
3d			75	230-235
3e			80	270-275
3f			79	260-265
3g			77	220-225
3h			75	230-235
3i			75	290-295
3j			75	250-255

[a] Isolated yield

The structures of synthesized compounds were confirmed by spectral analysis by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The structure of 2-(5-methylfuran-2-yl)quinoline-4-carboxylic acid **(3b)** was elucidated as below,



2-(5-methylfuran-2-yl)quinoline-4-carboxylic acid (3b)

In-silico studies on Pharmacological properties Based on the prediction in Table 3, the Lipophilicity of compounds **3a-3e, 3g - 3h** are shown less than five and compound **3f** and **3j** above five suggesting poor permeability across the cell membrane and which leads to one violation as per Lipinski's rule of five. And calculated percentages of absorption (% ABS) were found within 82 to 91%. Compounds **3c-3f**, **3h** and **3j** are found with the TPSA Values less 60 Å^2 and the good indication for the good permeability of the drug across the cellular plasma membrane. In the table 2 compounds **3a-3c** showed log S less than -4.00 and rest all compounds shown greater than -4.0.

Table 3: Molecular properties and Lipinski rule of five for the compounds (**3a-j**) & three reference drugs.

Lipinski's Parameters						TPSA[e] (Å²)	Volume	%ABS[f]	Log S[g]
ENTRY	HBA[a]	HBD[b]	MW[c]	miLogP[d]	Violations				
3a	4	1	239.230	2.778	0	63.331	203.857	87.151	-3.46
3b	4	1	253.257	3.000	0	63.331	220.418	87.151	-3.83
3c	4	1	252.273	2.497	0	55.125	224.217	89.982	-2.49
3d	3	1	328.165	4.446	0	50.191	240.174	91.684	-4.95
3e	3	1	275.307	4.581	0	50.191	249.706	91.684	-4.50
3f	3	1	309.750	5.260	1	50.190	249.706	91.684	-4.50
3g	6	1	339.347	3.268	0	77.893	298.926	82.127	-4.17
3h	3	1	299.329	4.820	0	50.191	266.281	91.684	-5.72
3i	4	2	315.328	4.529	0	70.419	274.298	84.705	-5.42
3j	3	1	349.389	5.931	1	50.191	310.272	91.684	-7.33
Chloroquine	3	2	319.880	5.000	1	28.160	313.120	99.285	-4.06
Moxifloxacin	7	2	401.440	0.390	0	83.800	350.620	80.089	-4.23
Irinotecan	10	1	586.690	4.100	1	114.210	530.67	69.598	-4.50

[a] Number of hydrogen bond accepotors (*n*-ON), [b]Number of hydrogen bond donors (*n*-OHNH), [c]Molecular weight, [d]Logarithm of partition coefficient between n-octanol and water(miLogP), [e]Topological polar surface area (TPSA), [f] Percent of absorption (%ABS), [g] Solubility (logs)

Molecular weight of all the compounds **3a-j** was found to be less than 500 and thus these molecules are anticipated to be easily transported, diffused and observed. Due to the presence of the pharmacophoric groups in the synthesized compounds **3a-j**, the drug scores of all compounds found to be a positive values and this indicates that the compounds contains predominantly fragments that are often present in most currently used drugs[37]. The drug score of all the compounds **3a-j** and reference drug are graphically represented in the **figure 2**. The global value predicted into a single numerical digit for each compound as a potential new drug candidate through the combined parameters like molecular weight, Lipophilicity, risk of toxicity, drug-likeness and solubility [38].

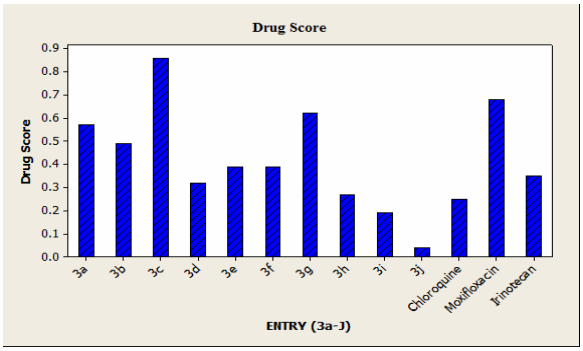


Figure 2 Graphical representation of Drug Scores of compounds **(3a-j)** and reference drugs.

Table 4: Toxicity risk for the 2-aryl/heteroaryl-quinoline-4-carboxylic acids (**3a-j**).

Entry	Potential risk[ab]			
	Mut	Tum.,	Irr.	Rep Eff.,
3a				
3b				
3c				
3d				
3e				
3f				
3g				
3h				
3i				
3j				
Chloroquine				
Moxifloxacin				
Irinotecan				

[a] Colors code for potential risk: Drug-conform, Middle risk, Undesired effects. (Mut.) Possible mutagenic, (Tum.) Tumorigenic, (Irr.) Irritant and (Rep. Eff.) Reproductive effective.

The possible pharmacological properties used to predict the drug-score of compounds 2-aryl/heteroaryl-quinoline-4-carboxylic acids **3a-j**, by employing OSIRIS software toxicity profile

evaluation was performed and the results are mentioned in Table 4. Exploring virtually the potential risk associated to different fragments of the synthesized aryl/heteroaryl-quinoline-4-carboxylic acids **3a-j**, It have been observed that all obtained and evaluated compounds **3a-h** found low biological risks without any few negative effect. The hydroxyl naphthalene group in the compound **3i** on the C-2 position of the quinoline scaffolds showed a moderate mutagenic risk and tumorigenicity risk. The anthracene group in the compound **3j** on the C-2 position found to have higher potential risk in terms of mitagenicity, tumorigenicity and irriative. The fragments and topology of the reference compound and compounds **3a-h** have shown drug-confirmation without any risks.

ADMET Prediction

The ADME &Toxicity predictions of the synthesized compounds (**3a-j)** have shown good Human intestinal absorption as the level of all compounds found to be zero. Solubility of compounds in water at $25^{O}C$ was predicted through aqueous solubility levels & lower the solubility compounds are favorable for good and complete oral absorption. [39] Accordingly the compound **3a** has good solubility level of 3 and for the remaining compounds **3b-3i** the solubility levels was found to be 2. Which clearly tell us they were moderately soluble (Table 5). All these results were compared against the reference Level (Table 1).

The blood brain barrier model predicts blood brain penetration of a molecule after oral administration. Among the synthesized compound **3j** was found to be extremely high in penetration. Whereas, the compounds **3d-3f, 3h, and 3i** shown moderately high BBB penetration. However the compounds **3a-3c, 3g** were low in BBB penetration.

ADMET plasma protein binding model predicts whether a compound is likely to be highly bound to carrier proteins in the blood. In the case of synthesized compounds **3g** was found to bind more than 90% to carrier proteins in the blood, whereas the compounds **3a-f, 3h-3j** exhibited greater than 95% binding capacity.

The ADMET hepatotoxicity indicates organ

Toxicity and the compounds can have adverse effect on liver. For instance, hepatotoxicity one indicates toxic nature of the compounds and zero indicates the non-toxic in nature.

Similarly the results for CYP2D6 probability shown, that the compound **3a** found to be non inhibitor during the metabolism via cytochrome P450 pathways [39].

Table 5: ADMET predictions of 2-aryl/heteroaryl-quinoline-4-carboxylic acids (**3a-j**).

Entry	BBB[a] Level	Absorption Level	Solubility Level	Hepatotoxicity	CYP2D6	PPB[b] Level	Unknown AlogP98
3a	2	0	3	1	0	2	0
3b	2	0	2	1	1	2	0
3c	2	0	2	1	1	2	0
3d	1	0	2	1	1	2	0
3e	1	0	2	1	1	2	0
3f	1	0	2	1	1	2	0
3g	2	0	2	1	1	1	0
3h	1	0	2	1	1	2	0
3i	1	0	2	1	1	2	0
3j	0	0	1	1	1	2	0

[a]BBB- Blood brain barrier, [b]PPB-Plasma Protein Binding.

Molecular docking studies

The structures of proteins selected for docking are malarial protein *Plasmodium falciparum lactate - dehydrogenase* (PDBID:1CET), Tuberculosis protein *Mycobacterium tuberculosis* (PDBID: 2X22) and for caner protein Human farnesyltransferase/geranylgeranyltransferase (PDB ID: 1S63) which were retrieved from PDB databank. The 3D protein structures shows 96% of quality factor and is more complex in nature. The resultant protein structures were used for active site and ligand binding site identification. Docking was carried out using Autodock tool.

Molecular docking result of malarial protein *Plasmodium falciparum* ldh (PDBID :1CET)

The X-ray diffraction structure of Plasmodium falciparum l- dehydrogenase with resolution of 2.05 À was docked with synthesized compounds 3a**-j** and Chloroquine as reference drug. Based on the results of molecular docking mentioned in the below table 6, the Plasmodium LDH protein interacts with reference drug Chloroquine binds through one hydrogen bond within active site amino acids ILE31having binding energy -4.30 kcal/mol. The compounds **3b** and 3d has five hydrogen bonds with strong interactions within active site amino acids THR97, THR97, GLY32, ILE31and GLY29:HN with binding energy of -8.03 kcal/mol and -8.29 Kcal/mol respectively as mentioned in the Table 7. Similarly compounds 3a, and **3e, 3g-3i** forms four hydrogen bonding interaction within the active site of amino acids ILE31, GLY29, GLY32, THR97, ARG109: and ARG171 with the binding energy -7.93, -7.25, -8.25, -8.81 and -9.00 kcal/mol respectively and this indicates compounds are more potent inhibition to *Plasmodium falciparum*. Compound 3c three hydrogen bond formations within the active site of amino acids with 8.64 kcal/mol, whereas compound **3j** found to have two hydrogen bonds with the least interaction energy of -9.62kcal/mol. Overall all synthesized compounds are found to have good inhibition capacities as compared to reference drug.

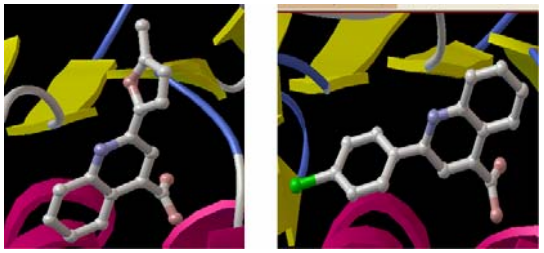


Figure 3 Docking images of compunds **3b** and **3d** with *Plasmodium falciparum* protein.

Table 6: Molecular docking results of compounds **3a-j** and reference drug Chloroquine with malarial protein *Plasmodium falciparum l- dehydrogenase* (PDBID:1CET).

Entry	Binding Energy (kcal/mol)	H-bonds	Interacting amino acids
3a	-7.93	4	ILE31, GLY29, GLY32, THR97.
3b	**-8.03**	**5**	THR97, THR, GLY32, ILE31, GLY29
3c	-8.64	3	ILE31, THR97, GLY32
3d	**-8.29**	**5**	GLY32, THR97, ILE31, THR97, GLY29
3e	-7.25	4	ARG109, ARG171, HIS248, ARG171
3f	-7.44	2	ASN197, VAL142,
3g	-8.25	4	GLY32, GLY29, THR97, ILE31
3h	-8.81	4	ILE31, THR97, THR97, GLY32
3i	-9.00	4	THR97, GLY32, ILE31, GLY29
3j	-9.62	2	ASN197, LYS198
Chloroquine	-4.30	1	ILE31

Molecular docking result of tuberculosis protein *Mycobacterium tuberculosis* (PDBID: 2X22)

The X ray diffraction structure of Tuberculosis protein *Mycobacterium tuberculosis* (PDBID: 2X22) with resolution of 2.10À was docked with synthesized compounds **3a-j** and Moxifloxacin as reference drug as results mentioned in the Table 7. Based on the molecular docking studies, the Mycobacterium tuberculosis protein interacts with Moxifloxacin binding through one hydrogen bond within active site amino acids ARG43 having binding energy -9.11 kcal/mol .

The compound **3g** has formed five hydrogen bonds with strong interactions within active site amino acids THR198, TYR158, ALA22, SER94 and ILE21 with binding energy of -8.36 kcal/mol. Similarly compounds **3a** and **3b** forms three hydrogen bonding interactions within the active site of amino

acids GLY96, ALA22, ALA22, and ILE21 with the binding energy -7.86, and -7.90 Kcal/mol respectively. Compounds **3c**, **3i** and **3j** found two hydrogen bond interactions within the active site of amino acids as mentioned in the Table 8. Whereas compounds **3d**, **3e 3f** and 3h found to have one hydrogen bonding interaction within the active site of amino acids THR196, LYS 165 and HIS265 with the binding energy of -8.34kcal/mol ,8.45 kcal/mol, -5.33 kcal/mol and -9.91kcal/mol respectively. Based on the results mentioned in Table 8 the synthesized compounds are potential to be a anti tuberculosis drug.

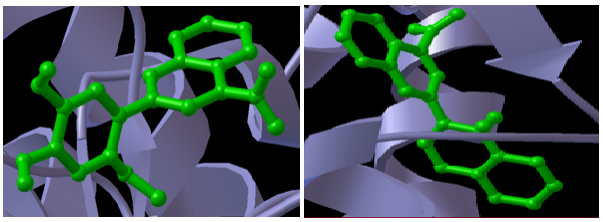


Figure 4 Docking images of compunds **3g** and **3a** and reference drug Moxifloxacin with Mycobacterium tuberculosis protein.

Table 7: Molecular docking results of compounds **3a-j** and reference drug Moxifloxacin with tuberculosis protein *Mycobacterium tuberculosis* (PDBID: 2X22).

Entry	Binding Energy (kcal/mol)	H-bonds	Interacting amino acids
3a	**-7.86**	**3**	GLY96 , GLY96 ALA22
3b	-7.9	3	GLY96 , ALA22 , ILE21
3c	-8.62	2	LYS165, THR196
3d	-8.34	1	THR196
3e	-8.45	1	LYS165
3f	-5.33	1	HIS265
3g	**-8.36**	**5**	THR198, TYR158, ALA22, SER94, ILE21,
3h	-9.14	1	TYR158
3i	-9.91	2	THR196, THR196
3j	-9.53	2	TYR158, LYS165,
Moxifloxacin	-9.11	1	ARG43

Molecular docking result of cancer protein *PFTase-GGTase*-I (PDB: 1S63)

The X ray diffraction structure Protein farnesyltransferase/geranylgeranyltransferase with resolution of 1.9 Å was docked with synthetic compounds **3a-j** and reference drug Irinotecan. Based on the results mentioned in the below table 9. Compounds **3a** and **3e** found four hydrogen bonds within the active site

of amino acids LYA164, LYS 353,ARG 291, LYS 294, ,HIS248 and ARG 291 with the binding energy of -6.82Kcal/mol, and -8.57Kcal/mol respectively. Similarly compounds **3b**, **3c**, **3f-3i** found to have 3 hydrogen bonds within the active site of amino acids and binding energy as mentioned in the table 8. Compounds **3d** and **3j** found to have one hydrogen bond each with the bonding energy of -7.23Kcal/mol and -8.36Kcal/mol respectively. Whereas reference drug found to have least binding energy of -8.72 with two hydrogen bonds within the active site os amino acids LEU295 and ARG 291. Thus the overall results show the compounds **3a-j** could be a good potential and more effective against tumor causing proteins.

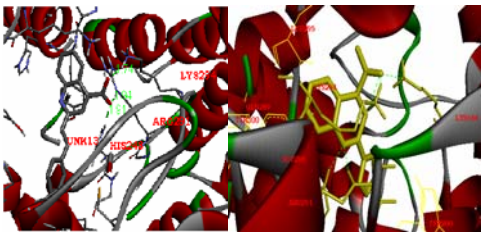


Figure 5 Docking images of compunds **3e and 3a** with protein PFTase-GGTase-I.

Table 8: Molecular docking results of compounds **3a-j** and reference drug Moxifloxacin with cancer protein PFTase-GGTase-I (PDB: 1S63).

Entry	Binding Energy (kcal/mol)	H-bonds	Interacting amino acids
3a	**-6.82**	**4**	LYA164, LYS 353, ARG 291, LYS 294
3b	-7.82	3	ARG291, HIS248, LYS294
3c	-6.52	3	ARG291, HIS248, LYS294
3d	-7.23	1	ARG 291
3e	**-8.57**	**4**	LYS294, ARG291, HIS 248, ARG 291
3f	-7.51	3	LYS 164, LYS 294, AGR 291.
3g	-6.79	3	HIS248, TYR 200, ARG291
3h	-8.17	3	HIS248, LYS164, LYS294
3i	-8.14	3	HIS248, TYR 166, ARG 291
3j	-8.36	1	TYR 361
Irinotecan	-8.72	2	LEU295,ARG 291

Conclusion

The novel 2-aryl/heteroaryl-quinoline-4-carboxylic acid derivatives (**3a-j**) were synthesized via simple and economically convenient method. The *in-silico* pharmacological studies were carried out on all the synthesized compounds. Interestingly most of the compounds obeyed Lipinski's rule of five. In addition the compounds exhibited membrane permeability and blood brain barrier with TPSA Values less 60. The toxicity studies reveals that except the compound **3j** all other compounds found to be safe and expected to show low or nil toxicity. ADMET properties predict all the compounds **3a-j** found to be within the desired levels of pharmacological requirements hence can be taken forward for further evaluation.

Excellent docking score was obtained against malarial protein for all compounds. Particularly the compound **3d** and **3b** forms each five hydrogen bonds with the interaction energy -8.29 kcal/mol and 8.03 kcal/mol respectively within active site of amino acids THR97:HG1, GLY32:HN, ILE31:HN,GLY29:HN and THR97:O. Against tuberculosis protein (2X22), **3b** and **3g** has shown good interaction by forming three and five hydrogen bonds respectively with the interaction energy of -7.90 kcal/mol and -8.36 kcal/mol within the active sites of amino acids THR198, TYR158, ALA22, SAR94, ILE21, GLY96. In the case of cancer protein (1S63), the compounds **3b** and **3e** have shown good interaction by forming three and four hydrogen bonds with the binding energy of -7.82 kcal/mol, and -8.57 kcal/mol respectively within the active site amino acid LYS294, ARG299, HIS248. Thus most of the quinolines evaluated have shown fair drugs score, bioavailability, and low potential risk. In particular the compound **3b** has shown promising binding result, excellent ADMET score to become potential drug.

Conflict of interests

Declared None

Acknowledgements

The authors are thankful to IISc Bangalore and University of Mysore, Mysore for providing spectral data and the authorities of Kuvempu University for providing the necessary facilities to carry out the present work.

References

[1] M. Sudharshan, T. Zehra, B. Sanjay, "Advances in the syntheses of quinoline and quinoline-annulated ring Systems," Current Organic Chemistry., 12, pp. 1116-1183, 2008.

[2] S.J. Benkovic, S. J. Baker, M. R. Alley, Y. H. Woo, Y. K. Zhang, T. Akama, W. Mao, J. Baboval, P. T. Rajagopalan, M. Wall, L. S. Kahng, A, Tavassoli, L. Shapiro, "Identification of borinic esters as inhibitors of bacterial cell growth and bacterial methyltransferases, CcrM and MenH," J. Med. Chem., 48, pp. 7468-7476, 2005.

[3] K. Majerz-Maniecka, B. Oleksyn, R. Musiol, B. Podeszwa, J. Polanski, Abstracts of Papers, Joint Meeting on Medicinal Chemistry, Vienna, Austria,; In Sci. Pharm. 2005, 73 (Suppl. 1), 194. June 20-23, 2005.

[4] L. Dassonneville, K. Bonjean, M.- C. De Pauw-Gillet, P. Colson, C. Houssier, J. Quetin-Leclercq, L. Angenot, S.Y. Ablordeppey, "Substituted indoloquinolines as new antifungal agents," Bioorg. Med. Chem. 10, pp. 1337-1346, 2002.

[5] K. Lackey and D.D. Sternbach, "Synthesis of substituted quinoline-4-carboxylic acids", Synthesis, 10, pp. 993-997, 1993.

[6] G.Verniest, X.Wang, N. De Kimpe, A. Padwa, "Heteroaryl Cross-Coupling as an Entry toward the Synthesis of Lavendamycin Analogues, A Model Study," J. Org. Chem. 75, pp. 424-433. 2010.

[7] K. Kaur, M. Jain, R. P. Reddy, R. Jain, "Quinolines and structurally related heterocycles as antimalarials." Eur. J. Med. Chem. 45, pp.3245-3264, 2010.

[8] S.K. Srivastava, A. Jha, S.K. Agarwal, R. Mukherjee, A.C. Burman, "Synthesis and structure-activity relationships of potent antitumor active quinoline and naphthyridine derivatives." Anticancer Agents Med Chem," 7(6), pp. 685-709, 2007.

[9] V. G.Granik, A. M. Zhidkova, S. S. Kiselev, R. G. Glushkov, A. I. Polezhaeva, M. D. Mashkovskii, **"**Synthesis and pharmacological activity of derivatives of quinoline and condensed quinolines." Pharm. Chem. J, 12, pp. 881-886, 1978.

[10] R. Dayam, LQ. Al-Mawsawi, Z. Zawahir, M. Witvrouw, Z. Debyser, N. Neamati, "Quinolone 3-carboxylic acid pharmacophore: design of second generation HIV-1 integrase inhibitors." J. Med. Chem, 51(5), pp. 1136-44, 2008.

[11] F. Shi, S. Zhang, S.S. Wu, Y. Gao, SJ. Tu, "A diversity-oriented synthesis of pyrazolo[4,3-f]quinoline derivatives with potential bioactivities via microwave-assisted multi-component reactions." Mol Divers, 15(2), pp. 497-505, 2011.

[12] Yeh-Long Chen, Yue-Ling Zhao, Chih-Ming Lu, Cherng-Chyi Tzeng, Jih-Pyang Wang, "Synthesis, cytotoxicity, and anti-inflammatory evaluation of 2-(furan-2-yl)-4-(phenoxy)quinoline derivatives. Part 4," Bioorg. Med. Chem, 14, pp. 4373-4378. 2006.

[13] C.M. Meléndez Gómez, V.V. Kouznetsov, M.A. Sortino, S.L. Alvarez,S.A. Zacchino," In vitro antifungal activity of polyfunctionalized 2-(hetero)arylquinolines prepared through imino Diels-Alder reactions." 16(17), pp. 7908-20, 2008.

[14] Wentao Gao, Jia Liu, Yun Jiang, Yang Li, "First synthesis of 2-(benzofuran-2-yl)-6,7-methylene dioxyquinoline-3-carboxylic acid derivatives," Beilstein. J. Org. Chem., 7, pp. 210-217. 2011.

[15] R. C. Elderfield, Heterocyclic compounds, Vol. 4. John-Wiley & Sons: New York, 1960, pp. 6-59.

[16] (a). W. Pfitzinger, "Chinolinderivateaus Isatinsäure." J. Prakt. Chem, 33, pp, 100, 1886. (b). W. Pfitzinger, J. Prakt. Chem, 38, pp, 582, 1888. (c). W. Pfitzinger, J. Prakt. Chem, 56, pp, 283, 1897.

[17] Yakaiah Erugu, Bhavanarushi Sangepu, Bharath Gandu,Gangagni rao Anupoju, Vatsala Rani Jetti1. "Design, synthesis of novel quinoline-4-carboxylic acid derivatives and their antibacterial activity supported by molecular docking studies." World J. Pharm. Pharm. Sci., 3(12), pp. 1612-1634, 2014.

[18] H.C. KiranKumar, K.M. Mahadevan, K.B. Manjappa, "High throughput one pot synthesis of 2-methylquinolines." Tetrahedron Lett, 54, pp.1368-70. 2013.

[19] P.J. Bindu, K.M. Mahadevan, T.R. Ravikumar, "An efficient one pot synthesis and photo-induced DNA cleavage studies of 2-chloro-3-(5-aryl-4,5-dihydroisoxazol-3-yl)quinolines." Bioorg. Med. Chem. Lett, 22(19), pp. 6095-8. 2012.

[20] V.P. Prabhakara, B.S. Sherigara, K.M. Mahadevan, H. Vijaykumar, "Synthesis and DNA cleavage studies of novel quinoline oxime esters." Synth. Commun." 40, pp. 2220-31. 2010

[21] A. Srinivasa, K.M. Mahadevan, H. Vijaykumar, "Imino Diels-Alder reactions: efficient synthesis of 2-Aryl-4-(2'-oxopyrrolidinyl-1')-1,2,3,4-tetrahydroquinolines catalyzed by antimony (III) Sulphate." Monatsh. Chem. 139, pp. 255-9. 2008.

[22] E. Siddalingamurthy, K.M. Mahadevan, N.M. Jagadeesh, M.N. Kumara, "Synthesis and docking study of 3-(N-alkyl/aryl piperidyl) indoles with serotonin-5HT, H1 and CCR2 receptors antagonist." Int. J. Pharm. Pharm. Sci, 6, pp. 475-82. 2014.

[23] N.M. Jagadeesh, K.M. Mahadevan, M.N.Kumara, N. Prashantha, "Synthesis and molecular docking study of N-alkyl/aryl-2-aryl indol-3-yl glyoxylamides as novel anticancer agents." Int. J. Pharm. Pharm. Sci, 6, pp. 921-6, 2014

[24] E. Siddalingamurthy, K.M. Mahadevan, N.M. Jagadeesh, M.N. Kumara, "Synthesis of novel γ-carboline derivatives and their insilico studies on 5HT1, H1 and CCR2 antagonist receptors." Int. J. Pharm. Pharm. Sci, 6(10), pp.548-54, 2014

[25] T.O. ShrungeshKumar, K.M. Mahadevan, M.N. Kumara, "Synthesis and cytotoxic studies of 2, 3-dimethylindoles and tetrahydrocarbazoles." Int. J. Pharm. Pharm. Sci, 6(2), pp. 137-40, 2014.

[26] T.O. ShrungeshKumar, K.M. Mahadevan, P.S. Sujan, M.N. Kumara, "Synthesis and molecular docking study of 2-aryl/heteroaryl-6-chloroquinoline-4-carboxylic acids with plasmodium ldh receptor protein," Int. J. Pharm. Pharm. Sci, 7(1), pp. 431-437, 2015.

[27] G. Vistoli, A. Pedretti, B. Testa, "Assessing drug-likeness- What are we missing?" Drug Discovery Today, 13, pp. 285-294, 2008.

[28] C.A. Lipinski, F. Lombardo, B.W. Dominy P.J. Feeney. "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings." Adv. Drug Delivery Rev, 23, pp 3-25, 1997.

[29] M.J. Ahsan, J. GovindaSamy, H. Khalilullah, S. Md. Nomani, P. Saraswat, R. Gaur, A. Singh, "Molecular properties prediction and synthesis of novel 1,3,4-oxadiazole analogues as potent antimicrobial and antitubercular agents." Bioorg. Med. Chem. Lett. (21), pp 7246-7250, 2011.

[30] Cheminformatics on the web. Available online: http://www.molinspiration.com/ (accessed on 04 April 2015).

[31] Organic Chemistry Portal. Available online: http://www.organic-chemistry.org/prog/peo/ (accessed on 04 April 2015).

[32] P. Ertl, B. Rohde, P. Selzer, "Fast calculation of molecular polar surface area as a sum of fragment based contributions and its application to the prediction of drug transport properties." J. Med. Chem, 43(20), pp. 3714-7. 2000.

[33] N.C. Desai, G.M. Kotadiya, A.R. Trivedi, "Studies on molecular properties prediction, antitubercular and antimicrobial activities of novel quinoline based Pyrimidine motifs." Bioorg. Med. Chem. Lett., 24, pp. 3126-3130, 2014

[34] Prija Ponnan, Shikhar Gupta, Madhu Chopra, Rashmi Tandon, S. Anil Baghel, Garima Gupta, K. Ashok Prasad, C. Ramesh Rastogi, Mridula Bose and G. Hanumantharao Raj. "2D-QSAR, Docking Studies, and In Silico ADMET Prediction of Polyphenolic Acetates as Substrates for Protein Acetyltransferase Function of Glutamine Synthetase of Mycobacterium tuberculosis." ISRN Structural Biology, 2013, pp. 1-12. 2013.

[35] Gade Deepak Reddy, K. N. V. Pavan Kumar, N. Duganath, Raavi Divya, Kancharla Amitha, "ADMET, Docking studies & binding energy calculations of some Novel ACE - inhibitors for the treatment of Diabetic Nephropathy." Int. J. Drug Dev. & Res, 4(3), pp. 268-282, 2012.

[36] G.M. Morris, D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew, A.J. Olson, "Automated docking using a Lamarckian Genetic Algorithm and empirical binding free energy function." J. Comput. Chem, 19, pp. 1639-62, 1998.

[37] Cledualdo Soares de Oliveira, Bruno Freitas Lira, Vivyanne dos Santos Falcão-Silva, Jose Pinto Siqueira-Junior, Jose Maria Barbosa-Filho, Petronio Filgueiras de Athayde-Filho, "Synthesis, Molecular Properties Prediction, and Anti-staphylococcal Activity of N-Acylhydrazones and New 1,3,4-Oxadiazole Derivatives." Molecules, 17, pp. 5095-5107, 2012.

[38] Bevan, R.S. Lloyd, "A highthroughput screening method for the determination aqueous drug solubility using laser nephelometry in microtiter plates." Anal. Chem, 72, pp. 1781–1787, 2000.

[39] R.G. Susnow, S.L. Dixon, "Use of robust classification techniques for the prediction of human Cytochrome P450 2D6 inhibition." J. Chem. Inf. Model, 43, pp. 1308- 1315, 2003.