Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 7, Issue 3, 2015

Original Article

SYNTHESIS, *IN VITRO* ANTIBACTERIAL, TOXICITY AND MOLECULAR DOCKING ANTICANCER ACTIVITY OF NOVEL *N*-[(2-CHLOROQUINOLIN-3-YL) METHYLIDENE]-2-ANILINE SCHIFF BASES

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

[a]Department of Post Graduate Studies and Research in Chemistry, School of Chemical Sciences, Kuvempu University, P. G. Centre, Kadur, Karnataka 577548, India, [b]Department of Medicinal Chemistry, Scientific Bio-Minds, Bangalore 560092, Karnataka, India
Email: mahadevan.kmm@gmail.com

Received: 13 May 2015, Revised and Accepted: 08 Jun 2015

ABSTRACT

Objective: Synthesis of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-aniline schiff bases **(3a-j)** and to study their *in vitro* antibacterial activity and *in silico* study towards cancer and malarial proteins.

Methods: Various *N*-[(2-chloroquinolin-3-yl) methylidene]-2-aniline schiff bases (3a-j) were synthesized by using 2-chloro-3-formyl quinoline and different anilines in presence of acetic acid as catalyst. All the new compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and LCMS analysis. The compounds 3a-j was subjected to antibacterial activity. *In silico* molecular properties were predicted using various online cheminformatic tools, the binding interactions with *Human DNA* topoisomerase I and *Plasmodium falciparum* lactate dehydrogenase proteins was studied through molecular docking and Irinotecan and mefloquine were used as reference drugs.

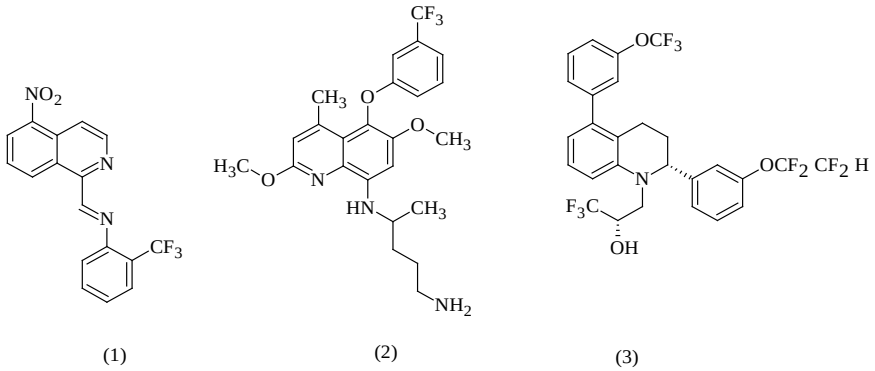
Results: Fairly good yield of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-aniline schiff bases (3a-j) were synthesized by convenient and economical procedure. The preliminary *in silico* pharmacokinetics study reveals that the compounds 3a-j shows excellent drug like property. The toxicity profile of compounds 3a-h was found safe. The compounds 3a-j was exhibited promising MIC values against the both *S. aureus and E. coli*. Similarly the docking results predict that the compound 3d shown highest interaction by forming two hydrogen bonds against the cancer protein with the interaction energy-20.696 kcal/mol. Compound 3c exhibits highest dock score of-45.703 kcal/mol with two hydrogen bonds against malarial protein.

Conclusion: From the results of docking studies of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-aniline schiff bases (3a-j), it has been concluded that the compounds were found to exhibit multifunctional lead property, hence these compounds are worth to be considered as potential lead molecules for further study.

Keywords: *N*-[(2-chloroquinolin-3-yl) methylidene]-2-aniline, 2-chloro-3-formyl quinoline, antibacterial, Molecular docking, ADMET.

INTRODUCTION

Quinoline Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry due to their wide range of biological activities like antimicrobial [1], anticancer [2] anthelmintic [3], anti-inflammatory [4]. Apart from medicinal applications, Schiff bases containing transition metals [5] have been reported as intermediates for the various organic syntheses, corrosion inhibitors [6], dyes, catalysts, pigments and polymer stabilizers [7], Schiff bases have found to be used in optical materials and wide array in the development of inorganic biochemistry [8]. Hence these compounds remain as a vital class of organic compounds, especially in the field of medicinal and pharmaceutical application [9-12] promoted researchers to synthesize various novel heterocyclic/aryl Schiff bases by eco-friendly methods. The schiff bases derived from Quinoline motif are biologically prominent active components [13]. Certain, schiff bases isolated from African plant Cryptolepine Sanguinolenta have been reported as potent antimalarial agents [14]. Further, many fluorinated compounds have been widely used for the treatment of various diseases and substitution of fluorine can alter the chemical properties and biological activity of many drugs [15]. The trifluoro methyl and its homologue C_nF_{2n+1} group into a heterocycle resulted into more potent activity due to the high lipophylicity of per fluoro alkyl substituents [16]. There are 4-[3-alkyl (aryl)-5-hydroxy-5-trifluoro methyl-4,5-dihidro-1*H*-pyrazol-1-yl]-7-chloroquinolines found to exhibits proven antimalarial activity against the Plasmodium falciparum parasite [17]. Rathelot et. al have reported functionalized 5-nitroisoquinoline Schiff base (1) as novel antimalarial agent [18] (fig. 1). On the other hand the-CF_3 (1,2), and-OCF_3 (3) (fig. 1) group containing compounds are found to be privileged functional groups which significantly influence on the various biological activities [19].



(1) (2) (3)

Fig. 1: Chemical structures of the biologically active molecules

Therefore, keeping in view of biological activities exhibited by various quinoline Schiff and in continuation of our effort to identify new quinoline based therapeutic agents (20-32), in the present investigation we report one pot synthesis of novel *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) which contains-CF_3 and-OCF_3 groups by using 2-chloro-3-formyl quinoline and various anilines. Thus the various *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) Schiff bases were synthesized by selecting-CF_3,-OCF_3 and-OPh substituted anilines. In this study, we envisage that molecular docking study is an ideal approach for discovering a new generation drugs for various ailments. Hence, instead of doing random biological testing, we approached the anticancer and antimalarial activity for all the newly synthesized *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) Schiff bases were carried out against the drug targets *Human DNA* topoisomerase I (PDB ID: 1T8I) and *Plasmodium falciparum* Lactate dehydrogenase (PDB ID: 1LDH) for cancer and malaria respectively. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and LCMS analysis.

MATERIALS AND METHODS

Chemistry

All chemicals were purchased from commercial sources and were used without further purifications. The TLC was done to monitor the progress of reactions using on alumina silica gel 60 F254 (Merck). The mobile phase was hexane and ethyl acetate (9:1 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 and 100 MHz, respectively) model spectrophotometer in $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are expressed as □ values relative to TMS as internal standard. Mass spectra were recorded on a Jeol SX 102=DA-6000(10 kV) FAB mass spectrometer.

A typical procedure for the synthesis of *n*-[(2-chloroquinolin-3-yl) methylidene]-2-(trifluoro methyl) aniline (3a)

An equimolar mixture of 2-chloro-3-formyl-quinoline (**1**) (1.064 g, 0.004 mol) and 2-(trifluoro methyl) aniline **2a** (0.37 ml, 0.004 mol) in ethanol with catalytic amount of acetic acid was stirred at room temperature for 6-7 hr at 25 °C. After the completion of the reaction, the separated solid was filtered and dried under vacuum to afford crude product. The crude product was purified by column chromatography using silica gel (60-120 mesh, petroleum ether: ethyl acetate, 9:1 v/v) furnished analytically pure *N*-[(2-chloroquinolin-3-yl) methylidene]-2-(trifluoro methyl) aniline **(3a) (**yield 80%). Similarly, all other derivatives **(3b-j)** were obtained**.**

Spectral data

(3a) *N*-[(2-chloroquinolin-3-yl) methylidene]-2-(trifluoro methyl) aniline

^{1}H NMR (400 MHz, $CDCl_3$): δ= 11.90 (s, 1H), 9.51 (s, 1H), 9.09 (s, 1H), 7.55-7.56 (m, 1H), 7.48 (t, *J* = 7.60 Hz, 2H), 7.28-7.30 (m, 2H), 7.13 (d, *J* = 8.00 Hz, 1H), 7.04 (d, *J* = 8.40 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.47, 117.11, 118.77, 120.25, 122.62, 124.88, 129.69, 130.01, 132.53, 133.72, 143.25, 152.09, 156.05, 163.98, 172.43, 189.52 ppm. MS: *m/z*=334.25(M^+).

(3b) *N*-[(2-chloroquinolin-3-yl) methylidene]-3-(trifluoro methyl) aniline

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.26 (s, 1H), 8.83 (s, 1H), 7.55-7.56 (m, 6H), 7.52 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.88, 116.12, 116.36, 118.01, 118.34, 122.93, 124.34, 129.74, 130.73, 132.42, 133.89, 143.03, 152.01, 156.57, 163.33, 171.90, 189.41 ppm. MS: *m/z*=334.25(M^+).

(3c) *N*-[(2-chloroquinolin-3-yl) methylidene]-4-(trifluoromethoxy) aniline

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.28 (s, 1H), 8.80 (s, 1H), 7.83-7.84 (m, 6H), 7.47-7.50 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.63, 115.66, 121.81, 123.37, 123.33, 124.36, 126.71, 127.29, 127.92, 128.10, 131.20, 137.83, 141.38, 149.93, 152.58, 159.22, 160.41 ppm. MS: *m/z*=350.12(M^+).

(3d) *N*-[(2-chloroquinolin-3-yl) methylidene]-3,5-bis (trifluoro methyl) aniline

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.29 (s, 1H), 8.79 (s, 1H), 8.04-8.08 (m, 2H), 7.85-7.87 (m, 2H), 7.29-7.49 (m, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 121.96, 123.83, 123.95, 124.05, 124.31, 124.94, 126.74, 127.46, 127.98, 128.19, 131.02, 132.76, 132.86, 137.83, 149.56, 149.94, 152.85, 160.98 ppm. MS: *m/z*=402.12(M^+).

(3e) *N*-[(2-chloroquinolin-3-yl)methylidene]-3,5-dimethyl aniline

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.59, 24.59, 120.39, 120.59, 124.73, 126.57, 127.69, 127.72, 128.31, 129.54, 131.80, 137.38, 139.46, 139.59, 148.78, 149.69, 152.58, 160.41, ppm. MS: *m/z*=294.17(M^+).

(3f) *N*-[(2-chloroquinolin-3-yl) methylidene]-4-methyl-3-(trifluoro methyl) aniline

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.73 (s, 1H), 9.45 (s, 1H), 9.05 (s, 1H), 7.78-7.89 (m, 5H), 7.39-7.41 (m, 1H), 2.49-2.53 (m, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.82, 117.17, 119.98, 124.63, 125.45, 126.37, 127.82, 127.59, 128.31, 129.62, 130.47, 131.30, 131.75, 137.58, 149.99, 146.43, 152.78, 160.11 ppm. MS: *m/z*=348.0(M^+).

(3g) 2-chloro-*N*-[(2-chloroquinolin-3-yl)methylidene]-4-(trifluoro methyl) aniline

^{1}HNMR (400 MHz, $CDCl_3$): δ = 10.27 (s, 1H), 8.81 (s, 1H), 7.89-7.92 (m, 3H), 7.85-7.87 (m, 2H), 7.53-7.54 (m, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 123.89, 124.60, 124.23, 126.34, 126.78, 127.52, 127.39, 128.07, 128.61, 130.49, 131.03, 137.38, 142.84, 149.59, 152.58, 160.23 ppm. MS: *m/z*=369.16(M^+).

(3h) *N*-[(2-chloroquinolin-3-yl) methylidene]-4-phenoxyaniline

^{1}H NMR(400 MHz, $CDCl_3$): δ = 11.86 (s, 1H), 10.26 (s, 1H), 9.22 (s, 1H), 9.00 (s, 1H), 8.82 (s, 1H), 7.97-7.99 (m, 2H), 7.93 (d, *J* = 7.60 Hz, 1H), 7.85-7.86 (m, 1H), 7.48-7.51 (m, 2H), 7.44 (t, *J* = 8.00 Hz, 1H), 7.25-7.26 (m, 1H), 7.09-7.14 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.93, 116.26, 118.87, 119.50, 119.90, 122.79, 123.30, 123.35, 123.61, 126.75, 129.45, 129.80, 130.66, 131.94, 133.83, 138.45, 139.26, 146.98, 154.01, 156.13, 163.71, 189.46 ppm. MS: *m/z*=358.15(M^+).

(3i) *N*-[(2-chloroquinolin-3-yl) methylidene]-2-phenoxyaniline

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.91 (s, 1H), 8.14-8.29 (m, 6H), 7.58 (d, *J* = 8.40 Hz, 2H), 7.43-7.45 (m, 2H), 7.36-7.37 (m, 1H), 7.27-7.28 (m, 1H), 7.14 (d, *J* = 8.40 Hz, 1H), 6.90-6.99 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.04, 117.93, 118.98, 119.70, 121.23, 122.34, 123.03, 123.63, 123.75, 126.71, 129.03, 129.66, 130.81, 131.78, 133.12, 134.09, 138.28, 140.54, 146.56, 163.51, 168.26, 189.23 ppm. MS: *m/z*=358.08(M^+).

(3j) 5-chloro-*N*-[(2-chloroquinolin-3-yl) methylidene]-2-phenoxy aniline

^{1}H NMR(400 MHz, $CDCl_3$): δ = 11.29 (s, 1H), 10.26 (s, 1H), 8.82 (s, 1H), 7.93 (d, *J* = 7.60 Hz, 2H), 7.87 (t, *J* = 7.60 Hz, 2H), 7.52-7.53 (m, 3H), 7.47 (t, *J* = 7.20 Hz, 1H), 7.23-7.32 (m, 1H), 7.12 (d, *J* = 7.60 Hz, 1H), 6.98 (d, *J* = 8.80 Hz, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 117.25 117.35, 120.52, 121.59, 122.73, 124.73, 126.57, 127.02, 127.51, 127.89, 128.07, 128.31, 128.34, 128.78, 131.90, 137.58, 140.03, 146.53, 149.79, 152.08, 157.50, 160.91 ppm. MS: *m/z*=393.11(M^+).

Antibacterial activity

The clinical isolations of bacterial strains were purchased from National Chemical Laboratory (NCL), PUNE. Antibacterial efficacies of the synthesized compounds were carried out on gram+ve bacteria *Staphylococcus aureus* [NCIM-5022] and gram-ve *Escherichia coli* [NCIM-5051] by using agar well diffusion method with minor modifications [33]. To assess the antibacterial activity through MIC of compounds (**3a-j**), culture plates were prepared using sterile agar media and swabbed with 100 µl of 24 hr mature broth culture of individual bacterial strains using Sterile L-shaped glass rod. Agar wells were prepared using sterile cork borer, 6 mm wells were made into the each Petri-plate. The 100 µl of each compound at various concentrations of 10, 20, 30, 40, 50, 60 and 80 µg/ml were added to agar wells in order to evaluate the minimum inhibitory

concentration at which bacterial growth inhibited. For comparative evaluation standard drug Ciprofloxacin (Hi Media, Mumbai, India) a positive control was used. Then, the MIC was calculated by measuring at each concentration after an incubation period of 36 hr at 37 °C.

***In silico* molecular property predictions**

The Synthesized compounds were checked to satisfy Lipinski's rule [34] of five using the Molinspiration virtual platform (http://www. molinspiration. com/cgi-bin/properties/) and also used to predict Bioactivity scores for various drug targets. OSIRIS program (http://www. organic-chemistry. org/prog/peo/) used to predict pharmacokinetics profile such as solubility, drug likeness/scores and toxicity potential of synthesized compounds (**3a-j**). Lipinski's rule of five is known as thumb rule that indicates whether a chemical can be orally active in humans for drug likeness [35] and the molecular property stated in the rule are very important for drug pharmacokinetics in the human body. The percentage of absorption (%ABS) is calculated by using %ABS=109-(0.345 X TPSA) [36] to express the degree of absorption and prediction of drug transport properties was predicted by using the parameter such as Molecular polar surface area (TPSA) [37]. The predictions are based on the fragments or functional group similarity for the query molecule with the *in vitro* and *in vivo* validated and compounds are analyzed [38] topologically with possible mutagenic (Mut.), tumorigenic (Tum.), and irritant (Irr.) and effective reproductive (Eff. Rep.) effects. Therefore, the color coded by yellow indicates medium risks; red color indicates high risk and green color indicates the compounds possess good drug-like properties.

Bioactivity of the synthesized compounds have been checked by calculating the activity score on various human Targets such as GPCR ligand, ion channel modulator, the nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor by using Molinspiration web based tool. Based on the scores of the compounds, the bioactivity has been predicted (39). For organic molecules the probability is if<-5.0 then inactive, if-5.0-0.0 then moderately active and if the bioactivity score is>0 then it is active, the results are mentioned in the table 5.

Pharmacokinetics properties

The absorption, distribution, metabolism, elimination and toxicity (ADMET) properties were estimated for the synthesized compounds (3a-j) by using the Discovery Studio 2.1 (Accelrys, San Diego, CA, USA) [40]. Therefore, the ADMET characteristics were quantitatively predicted for the compounds by a set of keys as mentioned in the table 1, these keys are the six mathematical models in built in the module [41].

Table 1: ADMET descriptors standard and keys

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 and pharmacophore modeling

To gain a better insight on the molecular mechanism of activity of these compounds, we tried to predict by using two methods of computational modeling; molecular docking and pharmacophore modeling. The binding interaction of synthetic compounds with appropriate drug targets can be explained through the following molecular docking studies, while pharmacophore modeling could predict active chemical features of these compounds that are responsible for its biological activity. All molecular modeling calculations were performed using Accelrys Discovery studio [42].

For our studies, a crystal structure of our drug targets *Human DNA topoisomerase I* and *Plasmodium falciparum Lactate dehydrogenase* are selected for cancer and malaria respectively. The best protein was selected based on Ramachandran plot analysis [43]. The high resolution x-ray crystal structures of the protein *human* DNA topoisomerase I in complex with the camptothecin and covalent complex with A 22 base pair DNA duplex (PDB ID: 1T8I) and Plasmodium falciparum l-lactate dehydrogenase complexed with NADH and oxamate (PDB ID: 1LDH) are retrieved from protein data bank [44].

The 3D structure of synthesis compounds was generated using catalyst algorithm in DS. Further, the compound preparations were carried out with constraint parameters such as ionization change, tautomer and isomer generation. By applying the force field CHARMm, minimization is carried out with the steepest descent method which follows by the conjugant gradient method till it satisfies the convergence gradient.

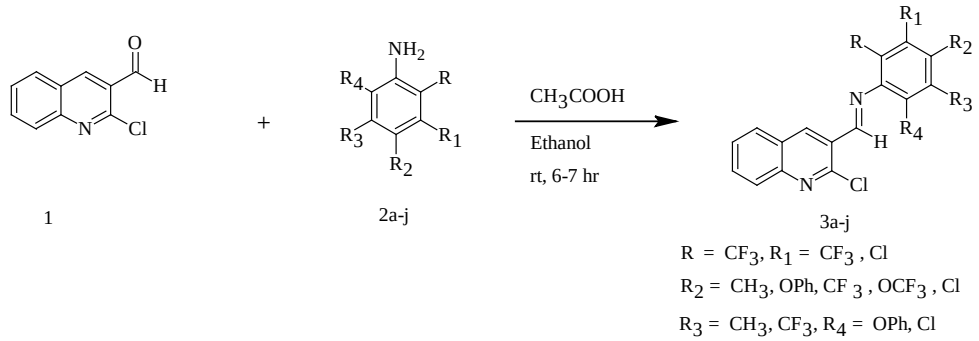
The CDOCKER and Ligand Fit modules in DS are used for molecular docking studies. CDOCKER uses a CHARMm-based molecular dynamics (MD) scheme to dock compounds into a receptor binding site to predict putative geometry of a protein-compound complex [45]. The CDOCKER docking simulations were performed to evaluate the binding mode of synthesized compounds **3a-j**, within an active site of *Human DNA topoisomerase I* (PDB ID: 1T8I). In order to evaluate our compounds docking affinities, docking studies are also carried out for the standard anti cancer Irinotecanin and the results are analyzed.

Ligand Fit is a shape-based method used to dock compounds into the active site of a protein. The determinations of the compound binding affinity are calculated based on the high Dock score of best conformation [46]. The Ligand Fit docking procedure was performed to evaluate the binding mode of synthesized compounds **3a-j**, within an active site of *Human DNA topoisomerase I*. The Docking scores were compared with standard antimalarial drug Mefloquine. The molecular modeling is carried out to construct a hypothetical pharmacophore model for the antitumor and antimalarial activity aiming to study the fitting of the designed compounds **3a-j** to the generated pharmacophores of target proteins *Human DNA topoisomerase I* and *Plasmodium falciparum Lactate dehydrogenase*. All pharmacophore modeling studies are performed using Catalyst in DS [47].

RESULTS AND DISCUSSION

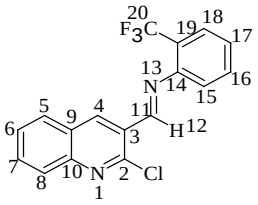
Chemistry

A common synthetic route was applied to obtain a new *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines **(3a-j)** Schiff's bases as shown in scheme 1. The 2-chloro-3-formylquinoline was used as key intermediate, with this commercially available appropriately substituted anilines, were condensed in the presence of catalytic amount of acetic acid in ethanol as solvent at 25 °C under stirring for 6-7 hr to get *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines **(3a-j)** Schiff bases and all the structures were confirmed by ^{1}H NMR, ^{13}C NMR and LCMS analysis.



Scheme 1: Synthesis of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j)

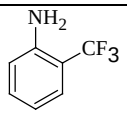
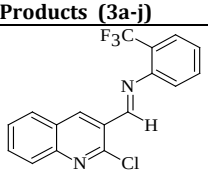
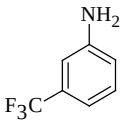
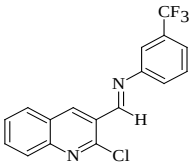
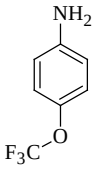
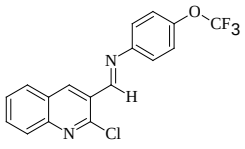
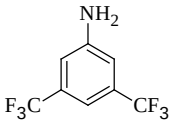
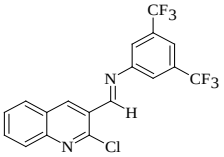
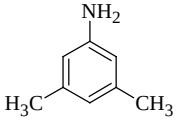
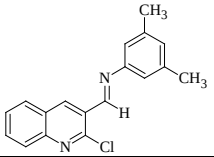
Initially, we examined the reaction of 2-chloro-3-formylquinoline 1 (1 mmol) with 2-(trifluoro methyl)aniline 2a (1 mmol) at room temperature stirring for 6 hours in the presence of catalytic amount of acetic acid in ethanol solvent The smooth reaction was occurred to generate the corresponding *N*-[(2-chloroquinolin-3-yl) methylidene]-2-(trifluoro methyl)aniline (3a) in 80% yield. The formation and the characterization of 3a was done as under

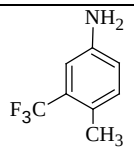
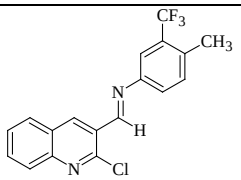
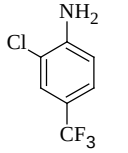
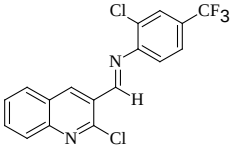
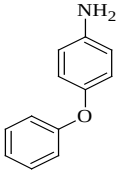
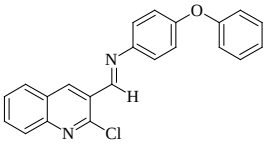
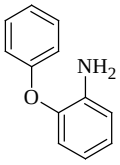
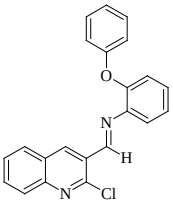
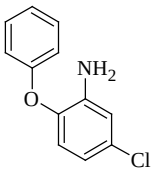
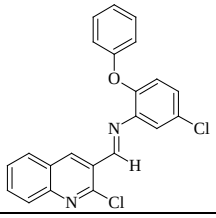


***N*-[(2-chloroquinolin-3-yl) methylidene]-2-(trifluoro methyl) aniline (3a)**

In ^{1}H NMR spectrum of 3a the peaks of aromatic protons have appeared in the expected region the numbers of protons are in accordance with the expected structure 3a. Triplet at δ = 7.48 ppm with coupling constant J = 7.6 Hz corresponds to C_6-H, doublet at δ = 7.04 ppm with coupling constant J = 8.4 Hz corresponds to C_{18}-H and another doublet at δ = 7.13 ppm with coupling constant J = 8.0 Hz corresponds to C_{15}-H. Additional support to elucidate the structures is obtained from ^{13}C NMR spectra of these compounds. The appearance of peak at δ = 116.47, 117.11, 118.77, 120.25, 122.62, 124.88, 129.69, 130.01, 132.53, 133.72, 143.25, 152.09, 156.05, 163.98, 172.43, 189.52 ppm corresponds to C_{20}, C_{19}, C_3, C_{15}, C_{18}, C_{17}, C_9, C_6, C_5, C_8, C_7, C_{16}, C_5, C_{14}, C_{10}, C_2, C_{11} carbon atoms respectively. The mass spectrum of 3a was recorded as additional evidence to the proposed structure and it exhibited M+1 peak at m/z 334.25. From all these spectral evidences the structure of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-(trifluoro methyl) aniline (3a) has been confirmed. Similarly, structures of all other derivatives (3a-j) were established and presented in experimental section and table 2.

Table 2: Physical data of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-aniline derivatives (3a-j)

Compounds	Substituted Anilines (2a-j)	Products (3a-j)	Yield[a](%)	M. P (°C)
3a			80	200-205°C
3b			80	270-275°C
3c			83	240-245°C
3d			85	250-255°C
3e			80	270-275°C

3f			83	260-265°C
3g			82	285-290°C
3h			80	185-190°C
3i			85	170-175°C
3j			80	215-220°C

a = Column Purified

Antibacterial activity

The newly synthesized *N*-[(2-chloroquinolin-3-yl) methylidene]-2-aniline derivatives (3a-j) were screened for their antibacterial activity against Gram+ve *S. Aureus* and Gram-ve *E. coli,* with standard drug Ciprofloxacin. The Determination of Minimum Inhibitory Concentration (MIC) is defined as the highest dilution or least concentration of the compounds that inhibit the growth of organisms. MIC values of the tested compounds are presented in Table-3. Based on the result, compounds 3a and 3i shown the MIC at 20.0 µg/ml against Gram+ve *S. aureus*, and the reference drug exhibits inhibition at 3.1 µg/ml. The compounds 3f, and 3i inhibit Gram-ve *E. coli* at MIC 10.0 µg/ml and compounds 3a, 3c, 3g at MIC 30.0 µg/ml, whereas standard Ciprofloxacin found to have 6.1 µg/ml against Gram-ve *E. coli.*

Table 2: Minimum Inhibitory concentration of the compounds (µg/ml)

Compounds	*S. aureus*	*E. coli*
3a	20.00	30.00
3b	40.00	60.00
3c	60.00	30.00
3d	60.00	60.00
3e	>80.00	60.00
3f	30.00	10.00
3g	>80.00	30.00
3h	80.00	>80.00
3i	20.00	10.00
3j	80.00	60.00
Ciprofloxacin	*3.10*	6.10

MIC of various compounds against Gram+ve *S. aureus*,

Gram-ve *E. coli*, expressed as µg/ml

***In silico* molecular property predictions**

Molecular properties of the synthesized compounds *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) are predicted by using Molinspiration online property calculation toolkit, the results are presented in the below table 4. According to, all the synthesized compounds (3a-j) were observed one violation and this clear violation is due to log p, all the synthesized compounds are found higher than 5 this may results poor permeability across the membrane, where as all three standard drugs found be under five and justifiable for oral use. Hydrogen bond acceptors and Donors are found within>10 and>5 as per Lipinski's rule of five. Molecular weight of all the compounds found to be less than 500 where as reference drug Irinotecan found to be higher than 500. Based on the results synthesized compounds are good diffusion and easily transported. Bioavailability, blood-brain barrier penetration and drug absorption including intestinal absorption are characterized as good descriptors through TPSA parameters [47]. The TPSA values of the synthesized compounds lies between 25.256 and 34.49 $Å^2$ hence, the compounds are proven to have good oral bioavailability as well as penetration through the blood-brain barrier [48]. For all the synthesized compounds % ABS are lies between 97.10 % to 100.29 %. Hence all the compounds found to exhibit good degree of absorption. Compounds 3a-j possess 2-4 rotational bonds, therefore all the synthesized compounds exhibits optimum conformational flexibility. Overall drug score was calculated in combination of drug-likeness, hydrophobicity (LogP), aqueous solubility (LogS), and toxicity risk parameters. The Oral hydrophobicity of the drugs is directly proportional the LogP value, ability of the drug to circulate longer in our body due to higher hydrophobicity.

The toxicity profile evaluation was performed to assess the pharmacological properties and predict the drug-score of the synthesized compounds 3a-j, potential risk has been associated

due to the presence of various fragments contained in the synthesized compounds 3a-j are virtually explored. Based on the below results in (table 5), irritating effects of compounds 3c and 3h are at medium risk and 3g shown to be high risk and the remaining compounds are found to be non toxic property. Therefore, the presence-OCF_3,-OPh and-CF_3 groups at para position in Schiff base fragments and topology of 3c, 3h and 3g shows medium and high risk towards biological toxicity compared with the remaining compounds (table 5). Hence the results indicates that all the synthesized compounds 3a-j would be safe and exhibit low or non toxic towards mutagenicity, Tumorigenicity and Reproductive effect.

Table 3: Calculated molecular properties and Lipinski's rule of five parameters for the *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j)

Lipinski's Parameters						TPSA (Å^2)	Volume	%ABS	nrotb	natoms
Compounds	HBA	HBD	MW	Mi Log P	Violations					
Rule	>10	>5	>500	>5.0	>1	-	-	-	-	-
3a	2	0	334.72	5.270	1	25.256	263.38	100.29	3	23
3b	2	0	334.72	5.294	1	25.256	263.38	100.29	3	23
3c	3	0	350.72	5.392	1	34.490	272.36	97.10	4	24
3d	2	0	402.72	6.142	1	25.256	294.67	100.29	4	27
3e	2	0	294.78	5.248	1	25.256	265.20	100.29	2	21
3f	2	0	348.75	5.695	1	25.256	279.94	100.29	3	24
3g	2	0	369.17	5.924	1	25.256	276.91	100.29	3	24
3h	3	0	358.82	6.177	1	34.490	312.47	97.10	4	26
3i	3	0	358.82	6.129	1	34.49	312.47	97.10	4	26
3j	3	0	393.27	6.783	1	34.490	326.01	97.10	4	27
Irinotecan	10	1	586.68	4.100	1	114.21	530.67	69.60	5	43
Ciprofloxacin	6	2	331.34	-0.70	0	74.569	285.46	83.27	3	24
Mefloquine	3	2	378.31	4.240	0	45.147	296.91	93.42	4	26

Log P=logarithm of the octanol/water partition coefficient; TPSA=topological polar surface area; MW=molecular weight; HBA=number of hydrogen bond acceptors; HBD = number of hydrogen bond donors; violations=number of violations of the Lipinski's rule of five; %ABS=absorption percentage; Log S= solubility

Table 5: Toxicity and Drug-relevant properties prediction for *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j)

Compounds	Potential risk[ab]				Drug-likeness	Drug-Score
	Mut.,	Tum.,	Irr.,	Rep Eff.,		
3a					-8.65	0.26
3b					-6.08	0.26
3c					-14.10	0.19
3d					-22.359	0.19
3e					-4.28	0.28
3f					-8.81	0.23
3g					-6.12	0.12
3h					-2.40	0.16
3i					0.74	0.31
3j					1.92	0.28
Irinotecan					0.07	0.35
Ciprofloxin					2.07	0.82
Melfoquine					-6.62	0.20

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

The bioactivity scores of the synthesized compounds *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) were predicted on the basis of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor and enzyme inhibitor were mentioned in table 6 as per the rule the observations are as follows.

Bioactivity scores towards GPCR ligand all the compounds were found to have moderate bioactivity (<0), whereas reference drug Irinotecan and Mefloquine found to be active with 0.33 and 0.45, Ciprofloxin found to be 0.12 for GPCR ligand. Ion channel modulator all compounds (3a-j) and reference drug Irinotecan and Ciprofloxin found moderate active. But reference drug Mefloquine found active for Ion channel modulator with value 0.21. For Kinase inhibitor all compounds (3a-j) and all three above mentioned reference drugs also found to be moderate active. Again for Nuclear receptor ligand and Protease inhibitor all compounds and reference drug Irinotecan and Ciprofloxin found moderate active, whereas Mefloquine found active with 0.30 and 0.36 score respectively. Enzyme inhibitor all compounds (3a-j) found to be moderate active where as all the reference compounds Molfoquine found active in enzyme inhibition.

Pharmacokinetics properties

The ADMET predictions of the synthesized compound 3a-j as mentioned in the table 7. Compounds 3a, 3b and 3e were shown good absorption, whereas compounds 3c, 3d and 3f-j found to have moderate intestinal absorption. Solubility of compounds in water at 25 °C was predicted through aqueous solubility levels and lower the solubility compounds are favorable for good and complete oral absorption [49]. The compounds 3a-j shown solubility levels 1 which was found to be very low (table 7). All these results were compared against the reference Level (table 1). All the compound 3a-j have shown high BBB penetration efficacy towards the blood brain barrier.

ADMET plasma binding predicts that the all the compounds 3a-j exhibited greater than 95% binding capacity to cross the membrane to plasma protein. ADMET hepatotoxicity indicates organ toxicity, which implies that the compounds except 3e all others are found to be toxic. For CYP2D6 probability, the result shown that the compounds 3h-i did not inhibit the CYP2D6 enzyme, but remaining compounds 3a-g found to inhibit CYP2D6 enzyme during metabolism via cytochrome P450 pathways [50].

Table 6: Predicted bioactivity scores for *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j)

Compounds	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
3a	-0.26	-0.22	-0.08	-0.18	-0.38	-0.12
3b	-0.25	-0.28	-0.02	-0.22	-0.41	-0.17
3c	-0.24	-0.22	-0.10	-0.13	-0.30	-0.16
3d	-0.19	-0.23	-0.01	-0.17	-0.31	-0.14
3e	-0.42	-0.48	-0.17	-0.48	-0.60	-0.24
3f	-0.28	-0.33	-0.05	-0.20	-0.45	-0.22
3g	-0.20	-0.29	-0.07	-0.28	-0.39	-0.17
3h	-0.24	-0.31	0.01	-0.23	-0.30	-0.11
3i	-0.23	-0.41	-0.09	-0.19	-0.30	-0.14
3j	-0.22	-0.40	-0.10	-0.20	-0.34	-0.17
Irinotecan	0.33	-0.45	-0.10	-0.15	0.02	0.54
Ciprofloxin	0.12	-0.04	-0.07	-0.19	-0.21	0.28
Melfoquine	0.45	0.21	-0.05	0.30	0.36	0.21

>0-active,-5.0-0.0-moderately active,<-5.0-inactive.

Table 7: ADMET Prediction of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j)

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

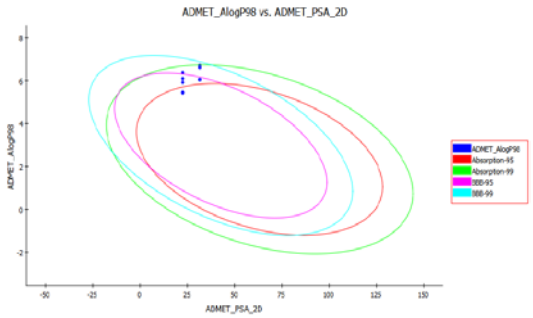


Fig. 2: ADMET descriptors, 2D PSA in À for each compounds plotted against their corresponding calculated atom-type partition coefficient (ALogP98)

Molecular docking and pharmacophore modeling of compounds 3a-j against cancer protein Human DNA topoisomerase I (PDB ID: 1T8I)

The synthesized *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) were tested for *in silico* docking studies within the compound binding poses of cancer protein of *Human DNA* topoisomerase I by using C-DOCKER and the results were interpreted in table 8. The reference molecule Irinotecan, interacting with *Human DNA* topoisomerase I, has docking scores of 26.645 (-Cdocker_Energy). As illustrated in table 8 the most potent ligand among the synthesized compound is *N*-[(2-chloroquinolin-3-yl) methylidene]-4-phenoxy aniline (3d) shows strong binding interaction with active site of ARG364 and ASN718 with high Cdocker energy score of 20.696 kcal/mol and forms two hydrogen bonds with the protein *Human* DNA topoisomerase (fig. 3a). Therefore, the hydrogen bonds are formed between chlorine atom of compound 3d interacting with hydrogen atom of nitrogen molecule of arginine 364 (A: ARG364:NH2–3d: Cl14) amino acid with a distance of 2.44300 Aºandoxygen atom of compound 3d interacts with the hydrogen atom of threonine 718 (A: THR718:HG1–3d: O21) with a distance of 2.45700 Aº, indicates more potent inhibitor of f *Human* DNA topoisomerase receptor. Pharmacophore model, for the protein Human DNA topoisomerase I, comprises, one HBA, one HBD and three hydrophobic features and almost all the compound has shown the fit score of 1.96 and the compound 3h shows a fit value of 2. But from the overall docking analysis and pharmacophore mapping, compound 3d is found as the lead compound as it shown stronger binding affinity compared to the other compounds. Fig. 3b shows the mapping of the compound 3d on to the pharmacophore model of Human DNA topoisomerase I.

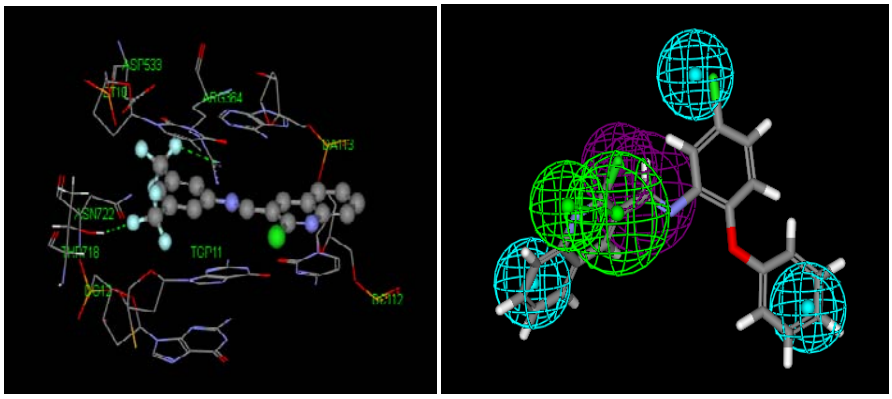
Table 8: Docking scores of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) with Cancer protein

Compounds	*Human* DNA topoisomerase I (PDB ID: 1T8I)	
	Cdocker_Energy	*Fit value*
3a	15.355	1.960
3b	19.365	1.960
3c	16.895	1.968
3d	20.696	1.960
3e	19.667	1.959
3f	17.521	1.960
3g	19.476	1.960
3h	18.985	2.000
3i	18.249	1.960
3j	20.267	1.960
Irinotecan	26.645	-

Molecular docking of pharmacophore modeling compounds 3a-j against malaria protein Plasmodium falciparum l-lactate dehydrogenase (PDB ID: 1LDH)

To study the binding modes of the *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) in the active sites of *Plasmodium falciparum* l-lactate dehydrogenase, molecular docking study was

performed by ligand fit program. Dock score is used to estimate the ligand-binding energies. The protein *Plasmodium falciparum* l-lactate dehydrogenase was docked with synthesized compounds (3a-j) and mefloquine as reference drug, results are summarized in table 9. The mefloquine reference drug was found to strong interaction with the protein structure with the Dock score of 47.234 kcal/mol (*Ligandfit Dock score).* The synthetic ligand *N*-[(2-chloroquinolin-3-yl) methylidene]-4-methyl-3-(trifluoro methyl)aniline (3c) having the highest dock score of 45.703 kcal/mol with two hydrogen bond formations with the ASN140 residue of protein 1LDH (fig. 4a). The first hydrogen bond is formed between the oxygen atom of ligand 3f interacting with the nitrogen atom of ASN140 with a distance of 2.212000 A° (A: ASN140:HD22-3c: O21) and second hydrogen bond is formed between the fluorine atom of compound 3c interacting with the amino acid residue ASN140 with a distance of 2.076000 A° (A: ASN140:HD22-3c: F23). Additionally, Pharmachopore model for protein of Plasmodium falciparum l-lactate dehydrogenase comprising two HBA, two HBD and two hydrophobic features and compound 3c is well fitted into the pharmacophore model with a fit value of 1.937 as shown in the below fig. 4b.

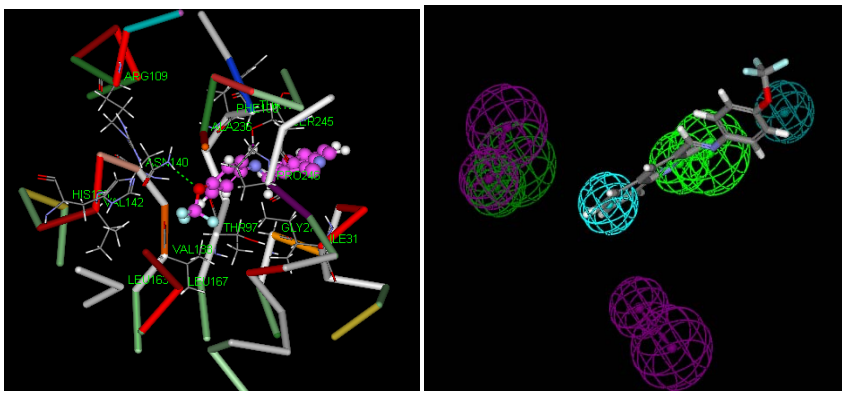


(a)-3d **(b)-3h**

Fig. 3: (a) Hydrogen bond interactions of compound 3d with *Human* DNA topoisomerase I and The green dotted lines represents the hydrogen bonds formations and green letters showing the amino acids involved in the bonding and compounds are shown in ball and stick model. (b) Pharmacophore mapping of compound 3h with Human DNA topoisomerase I Green color indicates hydrogen bond acceptor (HBA); cyan indicates hydrophobic (H) and magenta indicates hydrogen bond donor (HBD)

Table 8b: Docking scores of *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) with malarial protein

Compounds	***Plasmodium falciparum* (PDB ID: 1LDH)**	
	Ligand fit dock score	***Fit value***
3a	20.097	1.685
3b	24.367	1.891
3c	45.703	1.937
3d	20.509	1.892
3e	20.751	1.921
3f	25.555	1.899
3g	31.574	1.731
3h	41.991	1.904
3i	14.310	1.936
3j	6.614	1.532
Mefloquine	47.234	-



(a) 3C **(b)3c**

Fig. 4: (a) Docking image of compound 3c shown two Hydrogen bonds with Plasmodium falciparum l-lactate dehydrogenase. The green dotted lines represents the hydrogen bonds formations and green letters showing the amino acids involved in the bonding and compounds are shown in ball and stick model. (b) Pharmacophore mapping of compound 3c with Plasmodium falciparum l-lactate dehydrogenase. Green color indicates hydrogen bond acceptor (HBA); cyan indicates hydrophobic (H) and magenta indicates hydrogen bond donor (HBD)

CONCLUSION

Various *N*-[(2-chloroquinolin-3-yl) methylidene]-2-anilines (3a-j) Schiff bases containing biologically more significant-CF_3 and-OCF_3 groups were described. The *in vitro* study reveals that the synthesized compounds 3a-j found to inhibit *S. aureus* and *E. coli* with better MIC values. The *in silico* predictions of the synthesized compounds (3a-j) obeys Lipinski's rule of five. However, we observed one violation which results in the poor permeability across the membrane, remaining pharmacokinetics studies values was good to excellent with overall positive drug score which intern confirms the durglikeliness of the compounds. Nevertheless, compounds 3a and 3j were prone to plasma binding with >95 % and also found to be toxic for liver which needs certain modification in structure. Similarly among the test compounds 3a-j the compound 3d has shown strong binding interaction with protein *Human* DNA topoisomerase with an active site amino acid ARG364 and ASN718 with high Cdocker energy score of-20.696 kcal/mol. In the case of malarial protein *Plasmodium falciparum* the compound 3c had shown the highest dock score of-45.703 kcal/mol forming two hydrogen bonds. In conclusion, the compounds 3d and 3c are found to be promising pharmacophores for antimalarial and anticancer activity and hence can be considered for further evaluation.

CONFLICT OF INTERESTS

Declared None

ACKNOWLEDGMENT

The authors are thankful to IISc Bangalore, University of Mysore for providing spectral data and also thankful to Govt., Science College Tumkur University for providing the facility to carry out antibacterial activity. We also thank the authorities of Kuvempu University for providing the necessary facilities to carry out the present work.

REFERENES

1. Venkatesh P. Synthesis, characterization and antimicrobial activity of various schiff base complexes of Zn (II) and Cu (II) ions. Asian J Pharm Health Sci 2011;1:8-11.
2. Miri R, Razzaghi-asl N, Mohammadi MK. QM study and conformational analysis of an isatin Schiff base as a potential cytotoxic agent. J Mol Model 2013;19(2):727-35.
3. Avaji PG, Vinod Kumar CH, Patil SA, Shivananda KN, Nagaraju C. Synthesis, spectral characterization, *in-vitro* microbiological evaluation and cytotoxic activities of novel macrocyclic bis hydrazine. Eur J Med Chem 2009;44(9):3552-9.
4. Sondhi SM, Singh N, Kumar A, Lozach O, Meijer L. Synthesis, anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/benzoxazole derivatives and some Schiff's bases. Bioorg Med Chem 2006;14(11):3758-65.
5. Ershad S, Sagathforoush L, Karim-Nezhad G, Kangari S. Electrochemical behavior of N2SO Schiff-base Co (II) complexes in non-aqueous media at the surface of solid electrodes. Int J Electrochem Sci 2009;4(6):846-54.
6. Li S, Chen S, Lei S, Ma H, Yu R, Liu D. Investigation on some Schiff bases as HCl corrosion inhibitors for copper. Corros Sci 1999;41(7):1273-87.
7. Dhar DN, Taploo CL. Schiff bases and their applications. J Sci Ind Res 1982;41(8):501-6.
8. Tisato F, Refosco F, Bandoli G. Structural survey of technetium complexes. Coord Chem Rev 1994;135(136):325-97.
9. Sridhar SK, Pandeya SN, Stables JP, Ramesh A. Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur J Pharm Sci 2002;16:129-32.
10. Ashraf M, Wajid A, Mahmood K, Maah M, Yusoff I. Spectral Investigation of the activities of amino substituted bases. Orient J Chem 2011;27(2):363–72.
11. Golcu A, Tumer M, Demirelli H, Wheatley R. Cd(II) and Cu(II) complexes of polydentate Schiff base ligands: synthesis, characterization, properties and biological activity. Inorg Chim Acta 2005;358(6):1785-97.
12. Pandeya SN, Sriram D, Nath G, De Clercq E. Synthesis, antibacterial, antifungal and anti-HIV activity of Schiff and Mannich bases of isatin with N-[6-chlorobenzothiazol-2-yl]thiosemicarbazide. Indian J Pharm Sci 1999;61:358-61.
13. Rahul Pater V, Se Won Park. Synthesis of thiophenyl schiff bases via buchwald-hartwig coupling of piperazines to quinoline motif. Curr Org Synth 2014;11(4):621-5.
14. Dutta B, Some S, Ray JK. Thermal cyclization of 3-arylamino-3-(2-nitrophenyl)-propenal Schiff base hydrochlorides followed by triethyl phosphite mediated deoxygenation: a facile synthesis of quindolines. Tetrahedron Lett 2006;47(3):377-9.
15. Filler R. In: Banks RE. edotirs. Organofluorine chemicals and their industrial applications. London: Ellis Horwood; 1979.
16. Inouye Y, Tezuka K, Takeda W, Sugai S. Synthetic utilization of methyl 2-(F-methyl)-2-hydryl-F-propyl ether. Part III [1]. A simple one-pot preparation and derivatization of 2-alkylthio-5-(F-methyl)-6-fluoro-3,4-dihydro-4(3*H*)-pyrimidinones. J Fluorine Chem 1987;35(2):275-85.
17. Cunico W, Cechinel CA, Bonacorso HG, Martins MAP, Zanatta N, De Souza MVN, *et. al.* Antimalarial activity of 4-(5-trifluoro methyl-1H-pyrazol-1-yl)-chloroquine analogues. Bioorg Med Chem Lett 2006;16(3):649-53.
18. Rathelot P, Vanelle P, Gasquet M, Delmas F, Crozet MP, Maldonado J, *et al.* Synthesis of novel functionalized 5-nitroisoquinolines and evaluation of *in vitro* antimalarial activity. Eur J Med Chem 1995;6:503-8.
19. Jesmin M, Ali MM, Khanam JA. Antitumour activities of some Schiff bases derived from benzoin, salicylaldehyde, amino phenol and 2,4 dinitrophenyl hydrazine. Thai J Pharm Sci 2010;34:20-31.
20. Akranth M, OmPrakash T, Rikta S, Mohammad RA, Sandeep S, Akhter M, *et al.* Quinoline: a versatile heterocyclic. Saudi Pharm J 2013;21:1-12.
21. Kiran Kumar HC, Mahadevan KM, Manjappa KB. High throughput one pot synthesis of 2-methylquinolines. Tetrahedron Lett 2013;54:1368-70.
22. Bindu PJ, Mahadevan KM, Ravikumar Naik TR. 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 2012;22(19):6095-8.
23. Bindu PJ, Mahadevan KM, Ravikumar Naik TR. Sm(III)nitrate-catalyzed one-pot synthesis of furano[3,2c]-1,2,3,4-tetrahydroquinolines and DNA photocleavage studies. J Mol Struct 2012;1020:142-7.
24. Kirankumar HC, Mahadevan KM, Prabhakara VP, Srinivasa A. One pot Synthesis of medicinally important cis-2-Methyl-4-amino substituted-1,2,3,4-tetrahydroquinoline. Chin J Chem 2012;30:534-40.
25. Bindu PJ, Mahadevan KM, Satyanarayan ND, RavikumarNaik TR. Synthesis and DNA cleavage studies of novel quinoline oxime esters. Bioorg Med Chem Lett 2012:22:898-900.
26. Prabhakara VP, Sherigara BS, Mahadevan KM, Vijaykumar H. Synthesis and DNA cleavage studies of novel quinoline oxime esters. Synth Commun 2010;40:2220-31.
27. Srinivasa A, Mahadevan KM, Vijaykumar H. 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 2008:139:255-9.
28. Siddalingamurthy E, Mahadevan KM, Jagadeesh NM, Kumara MN. Synthesis and docking study of 3-(N-alkyl/aryl piperidyl) indoles with serotonin-5HT, H1 and CCR2 receptors antagonist. Int J Pharm Pharm Sci 2014;6:475-82.
29. Jagadeesh NM, Mahadevan KM, Kumara MN, Prashantha N. Synthesis and molecular docking study of N-alkyl/aryl-2-aryl indol-3-yl glyoxylamides as novel anticancer agents. Int J Pharm Pharm Sci 2014;6:921-6.
30. Jagadeesh NM, Mahadevan KM, Preenon B. Synthesis, molecular docking and fluorescent properties of novel (E)-3-(9-ethyl-9H-carbazol-3yl)-1-phenylprop-2-en-1-ones. Int J Pharm Pharm Sci 2014;6(10):317-25.
31. Siddalingamurthy E, Mahadevan KM, Jagadeesh NM, Kumara MN. Synthesis of novel γ-carboline derivatives and there in silico studies on 5HT1, H1 and CCR2 antagonist receptors. Int J Pharm Pharm Sci 2014;6(10):548-54.

32. Shrungesh Kumar TO, Mahadevan KM, Kumara MN. Synthesis and cytotoxic studies of 2,3-dimethylindoles and tetrahydrocarbazoles. Int J Pharm Pharm Sci 2014;6(2):137-40.
33. Tepe B, Donmez E, Unlu M, Candan F, Daferera D, Vardar-Unlu, *et al.* Antimicrobial and antioxidative activities of the essential oils and methanol extracts of Salvia cryptantha (Montbret et Aucher ex Benth.) and salvia multicaulis (Vahl). Food Chem 2004;84(4):519-25.
34. Hou TJ, Xu XJ. Recent development and application of virtual screening in drug discovery: an overview. Curr Pharm Des 2004;10:1011-33.
35. Lipinski CA, Lombardo L, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Delivery Rev 2001;46:3-26.
36. Zhao YH, Abraham MH, Lee J, Hersey A, Luscombe CN, Beck G, *et al.* Rate-limited steps of human oral absorption and QSAR studies. Pharm Res 2002;19:1446-57.
37. Desai NC, Kotadiya GM, Trivedi AR. Studies on molecular properties prediction, antitubercular and antimicrobial activities of novel quinoline based pyrimidine motifs. Bioorg Med Chem Lett 2014;24:3126-30.
38. Actelion's property explorer, Thomas Sander, Actelion's Pharmaceuticals Ltd, Gewerbestrasse 16, Allschwil, Switzerland; 2001. p. 4123.
39. Proudfoot JR. Drugs, leads, and drug-likeness: an analysis of some recently launched drugs. Bioorg Med Chem Lett 2002;12(12):1647-50.
40. Discovery Studio, version 2.1: Accelrys, Inc: San Diego, CA, USA; 2012.
41. Prija P, Shikhar G, Madhu C, Rashmi T, Anil SB, Garima G, *et al.* 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 Struct Biol 2013;12:1-12.
42. Discovery Studio, version 3.5: Accelrys, Inc: San Diego, CA, USA; 2012.
43. Laskowski RA, Rullmannn JA, MacArthur MW, Kaptein R, Thornton JM. AQUA and Procheck-NMR: programs for checking the quality of protein structures solved by NMR. J Biomol NMR 1996;8(4):477-86.
44. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, *et al.* 2000. The protein data bank. Nucleic Acids Res 2000;28:235-42.
45. Wu G, Robertson DH, Brooks CL, Vieth M. Detailed analysis of grid-based molecular docking: A case study of Cdocker—A CHARMm-based MD docking algorithm. J Comput Chem 2003;24:1549-62.
46. Venkatachalam CM, Jiang X, Oldfield T, Waldman M. Ligand fit: a novel method for the shape-directed rapid docking of ligands to protein active sites. J Mol Graph Model 2003;21:289-307.
47. Chohan ZH, Youssoufi MH, Jarranpour A, Hadda TB. Identification of antibacterial and antifungal pharmacophore sites for potent bacteria and fungi inhibition: indolenyl sulfonamide derivatives. Eur J Med Chem 2010;45:1189-99.
48. Romero BAR, Kouznetsov VV, Zacchino SA. Synthesis and *in vitro* evaluation of antifungal properties of some 4-Aryl-3-Methyl-1,2,3,4-Tetrahydroquinolines Derivatives. Univ Sci 2015;20(2):177-89.
49. Bevan CD, Lloyd RS. A high throughput screening method for the determination of aqueous drug solubility using laser nephelometry in microtiter plates. Anal Chem 2000;72:1781-7.
50. Susnow RG, Dixon SL. Use of robust classification techniques for the prediction of human Cytochrome P450 2D6 inhibition. J Chem Inf Comput Sci 2003;43:1308-15.