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Synthesis, characterization, theoretical, anti-bacterial and molecular docking studies of quinoline based chalcones as a DNA gyrase inhibitor

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ABSTRACT

A series of fourteen ($\mathbf{A_1}$–$\mathbf{A_{14}}$) new qunioline based chalcones were synthesized by condensing 2,7-dichloro-8-methyl-3-formyl quinoline with acetophenone and acetylthiophenes, and subsequently characterized by IR, NMR and Mass spectroscopy. All the compounds were screened for antibacterial activities and found potentially active antibacterial agents. Bioassay, theoretical and dockings studies with DNA gyrase (the enzyme required for super coiling of DNA of bacteria) results showed that the type and positions of the substituents seemed to be critical for their antibacterial activities. The bromo and chloro substituted chalcone displayed high anti-bacterial activity. The $\mathbf{A_4}$ and $\mathbf{A_6}$ showed high interaction with DNA gyrase, contributing high free binding energy (ΔG −8.18 and −8.88 kcal).

1. Introduction

Chalcones are α,β-unsaturated ketones, chalcones constitute an important class of natural products that serve as the precursor for synthesis of various heterocyclic compounds like pyrimidines, imidazoles [1], pyrazoles [2], 2-pyrazolines [3,4], and flavonoids [5]. Chalcones, either natural or synthetic, are known to exhibit various biological activities such as anti-inflammatory [6,7], antifungal [8–11], antioxidant [12–15], antimalarial [11–19], anti-tuberculosis [20], analgesic [21], anti-human immunodeficiency virus (HIV) [22], and antitumor activities [23,24]. Some of them also act as anticancer [25], antiviral [26], and anti-AIDS agents [27]. Quinoline-based chalcones have been reported to possess antimalarial activity [28]. Chalcones as well as some quinoline derivatives have already been recognized for their antimicrobial [29,30], and antileishmanial activities [31–33].

Chalcones are considered the precursors of naturally-occurring compounds flavonoids and isoflavonoids, but their true importance is extended in two branches: (i) the biological activity associated with them (including anti-inflammatory, antimitotic, anti-leishmanial, anti-invasive, anti-tuberculosis, anti-fungal, anti-malarial, anti-tumor), and (ii) anti-oxidant properties [5,34–43].

In the present study we have incorporated quinoline nucleus in the newly synthesized anti-bacterial drugs which act as DNA gyrase inhibitor and efflux pumps inhibitor in bacteria [44,45]. To increase drug like properties of our compounds ($\mathbf{A_1}$–$\mathbf{A_{14}}$) we have introduced benzene and thiophene rings which contained high lipophilic groups like bromo, and chloro that assist the drug molecule to enter into bacterial cell very easily. We have also changed the position of substituent groups on benzene and thiophene rings in order to find out the substituent effect on antimicrobial activities (Fig. 1).

2. Results and discussion

The precursor 2,7-dichloro-8-methyl-3-formyl quinoline was prepared by the previously reported method [46]. Synthesis of the title compounds ($\mathbf{A_1}$–$\mathbf{A_{14}}$) were prepared through Claisen–Schmidt reaction [36,42] by the condensation of formyl quinoline with commercially available methyl aryl ketones in the presence of sodium hydroxide (Scheme 1 and Chart 1). All the newly synthesized chalcones were in full agreement with the proposed structures. The E-configuration was confirmed by the spectral data (IR, ^{1}H NMR and MS). Configuration of the double bond was ascertained by coupling constants in ^{1}H NMR.

2.1. Antibacterial activity

Antibacterial activities of the synthetic compounds were tested against six bacterial species including *Escherichia coli* (Gram-negative), *Klebsiella aerogenes* (Gram-negative), *Salmonella typhimurium*

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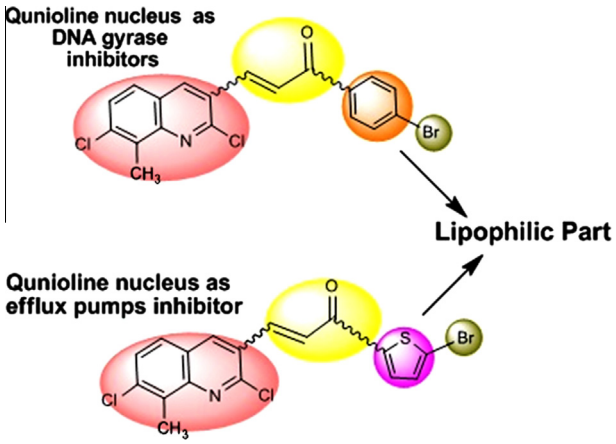


Fig. 1. Representation of different active part of newly synthesized drug against bacteria.

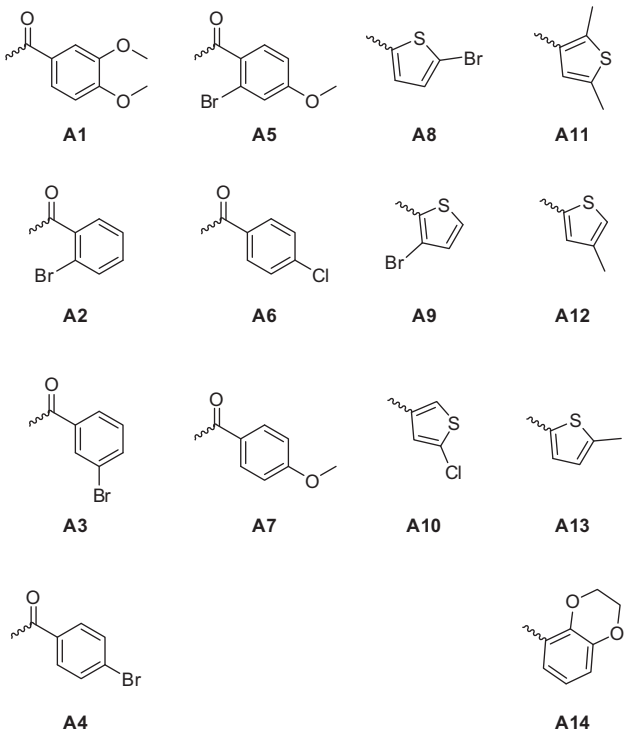


Chart 1. Methyl Aryl (Ar) Moiety of Aromatic Ketones ($\mathbf{A_1}$–$\mathbf{A_{14}}$).

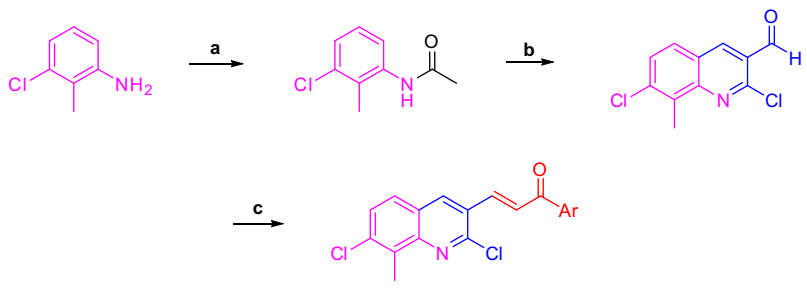
(Gram-negative), *Staphylococcus aureus* (Gram-positive), *Streptococcus pyogenes* (Gram-positive) and *Bacillus subtilis* (Gram-positive) by using method of Minimum Inhibitory Concentration (MIC). A commercial antibacterial capsule Chloramphenicol and ciprofloxacin were used as a positive control for its comparative study with all synthetic compounds.

The bioactivity results indicate that substituted phenyl derivatives ($\mathbf{A_2}$ and $\mathbf{A_3}$) are less active than $\mathbf{A_4}$ (IC_{50} = 0.125 mg/ml against *S. aureus, S. aureus* and *E. coli,* IC_{50} = 0.5 mg/ml against *Klebsiella aerogenes*, *S. typhimurium* and *B. subtilis*). The only difference between these molecules is the position of bromine on the benzene ring. The activity is decreased considerably by the introduction of Br group at 3- and 2-positions ($\mathbf{A_2}$ and $\mathbf{A_3}$, respectively) of phenyl ring whereas the activity is relatively increased on moving the Br substituent to 4-position ($\mathbf{A_4}$) of phenyl ring. Conversely, replacing the bromo by chloro ($\mathbf{A_6}$), and methoxy at 4-position of phenyl ring ($\mathbf{A_7}$) results in decrease activity. This may be attributed to the greater hydrophobic effect of bromo group, than chloro, and methoxy at 4-position.

The substituted hetero-aryl derivatives $\mathbf{A_8}$, $\mathbf{A_{14}}$ and $\mathbf{A_{10}}$ have shown promising antibacterial activities against all the bacterial strains. Among the compounds, substituted thiophenyl derivatives ($\mathbf{A_{11}}$, $\mathbf{A_{12}}$, $\mathbf{A_{13}}$,) exhibit almost equivalent antibacterial activities to that of the standard (Table 1). Activity decreases considerably by the substitution of methyl on thiophene ring ($\mathbf{A_{11}}$, $\mathbf{A_{12}}$, and $\mathbf{A_{13}}$). Incorporation of chlorine at 5-position of thiophene ring ($\mathbf{A_{10}}$) enhanced the activity to a reasonable extent; it is further increased by the incorporation of another bromine atom at 5-position ($\mathbf{A_8}$). However, incorporation of bromo group at 2-positions ($\mathbf{A_9}$) decreases activity. The incorporation of a second methyl group at 2-position ($\mathbf{A_{11}}$) have decreases the activity than that of mono substituted one ($\mathbf{A_{12}}$, $\mathbf{A_{13}}$). In general, activity is enhanced by the substitution of aromatic rings with electron withdrawing groups and is suppressed by the incorporation of electron donating methyl groups. No systematic change has been observed in antibacterial activities for the rest of the compounds. All the above results are also supported by theoretically calculated LogP and bioassay studies.

2.1.1. DNA gyrase inhibitory assay

To understand the mechanism by which the quinoline based chalcones derivatives induced the anti-bacterial activity, the inhibitory activity of the selected compound were performed against the DNA gyrase. The DNA gyrase was isolated from *S. aureus*, the result were shown in Table 2. The compound $\mathbf{A_4}$ and $\mathbf{A_6}$ with strong anti-bacterial activities powerfully inhibited the *S. aureus* DNA gyrase with IC_{50} of 0.14 and 0.16 μg/ml respectively. There was good agreement between the docking experiment and DNA gyrase inhibitory MIC values, indicating that the inhibition of the bacterial growth is due to the inhibition of DNA gyrase by quinoline based



Scheme 1. Reaction protocol for the synthesis of chalcones ($\mathbf{A_1}$–$\mathbf{A_{14}}$). (a) AcOH, H_3PO_4, reflux, 4–6 h, (b) $POCl_3$, DMF, 80 °C, (c) methyl aryl ketones, NaOH, rt, 2 h.

Table 1
Anti-bacterial Activities of the Chalcones (**A_1–A_{14}**) (IC_{50} mg/ml).

Compound	*Bacillus subtilis*	*Staphylococcus aureus*	*Streptococcus pyogenes*	*Escherichia coli*	*Klebsiella aerogenes*	*Salmonella typhimurium*
A-1	1.0	1.0	1.0	1.0	1.0	1.0
A-2	1.0	1.0	1.0	1.0	1.0	1.0
A-3	1.0	1.0	0.5	1.0	0.5	1.0
A-4	0.5	0.125	0.125	0.125	0.5	0.5
A-5	0.5	0.5	0.5	0.5	0.5	0.5
A-6	0.5	0.125	0.5	0.5	0.125	0.5
A-7	1.0	1.0	1.0	1.0	1.0	1.0
A-8	0.5	0.125	0.125	0.5	0.5	0.125
A-9	1.0	1.0	1.0	1.0	1.0	1.0
A-10	0.125	1.0	0.5	0.5	0.5	0.5
A-11	1.0	1.0	1.0	0.5	1.0	1.0
A-12	1.0	0.5	1.0	1.0	0.5	1.0
A-13	1.0	0.5	1.0	0.5	1.0	0.5
A-14	0.5	0.125	0.125	0.125	1.0	1.0
Chloramphenicol	1.0	1.0	1.0	1.0	1.0	1.0
Ciproflxoacin	1.0	0.5	1.0	0.5	1.0	1.0

Table 2
The inhibitory analysis of selected chalcones against DNA gyrase.

Compounds	*S. aureus* DNA gyrase $IC_{50\mu g/ml}$
A-4	0.14
A-6	0.16
A-7	5.15
A-8	1.01
A-14	0.95
Ciprofloxacin	0.22

chalcones. The inhibitory assay of DNA gyrase are good in agreement with docking experiments.

2.1.1.1. Molecular descriptors-based SAR studies of chalcones. From the data obtained by the theoretical evaluation of the ADME properties, one can notice that hybrid compounds **A_1–A_{14}** do not break any point of the Lipinski's rule of five, making them promising leads for drug candidates [47]. LogP (Table 3) values are compatible with those described as a predictive indicator of a drug's capacity for membrane penetration [48]. The field template showed a good similarity of the most active chalcone **A_4** with quinoline based drug ciproflaoxcin as shown in Fig. 2.

For the comprehension of three-dimensional microscopic interactions and binding between a ligand and a receptor, a detail analysis in SAR is important in drug design and synthesis. A number of chemical parameters are reported to be responsible for their molecular interactions. Although many reports on the structure activity relationships based on the biological properties of chalcones have been the subject of a large number of investigations

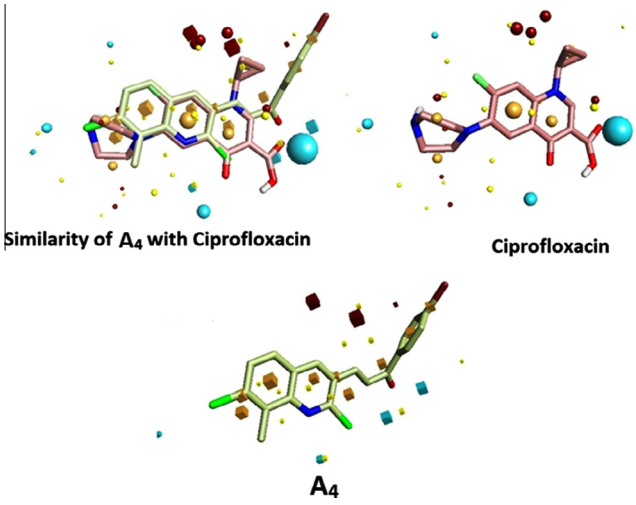


Fig. 2. Representing the similarity of **A_4** with ciprofloxacin calculated by Field Templater.

[49,50], but the present study is the first report of its nature on the antibacterial activity of chalcones against different bacterial strain types of molecular descriptors. Calculations were performed by software package, Namely ACDlabs, in order to derive a quantitative relation between bactericidal activity and structural properties. The values of the calculated the parameters are given in Table 3.

Table 3
Calculated molecular discriptors.

Compounds	*R*	(Log*P*)	LogKoc (Koc)	LogBCF (BCF)	No. of H-donor	No. of H-acceptor	PSA
A-1	3,4-OCH_3	5.72	4.1(30712.00)	4.1(13040.45)	0	4	48.40
A-2	2-Br	5.83	4.5(35322.38)	4.2(15854.16)	0	2	29.94
A-3	3-Br	6.14	4.9(77083.59)	4.7(47165.41)	0	2	29.95
A-4	4-Br	6.42	4.6(44596.77)	4.9(74054.95)	0	2	29.96
A-5	2-Br, 4-OCH_3	6.12	4.7(32737.98)	4.4(26168.79)	0	3	39.19
A-6	4-Cl	6.24	4.5(20229.20)	4.8(59355.09)	0	2	29.96
A-7	4-OCH_3	5.65	4.4(28074.36)	4.1(11502.72)	0	3	39.19
A-8	3-Br	6.14	4.7(51823.04)	4.4(27084.16)	0	2	58.20
A-9	2-Br	5.38	4.3(20229.20)	3.9(7277.05)	0	2	58.20
A-10	5-Cl	6.00	4.6(43889.70)	4.3(21473.55)	0	2	58.20
A-11	2,5-CH_3	5.64	4.7(48218.08)	4.4(24448.88)	0	2	29.09
A-12	4-CH_3	5.89	4.4(24667.63)	4.0(9600.87)	0	2	29.08
A-13	3-CH_3	5.54	4.4(24667.63)	4.0(9600.87)	0	2	58.20
A-14	1,4-Benzodioxane	5.65	4.4(26078.77)	4.1(11505.26)	0	4	48.22

Table 4
Summary of calculated binding parameters of chalcones ($\mathbf{A_1}$–$\mathbf{A_{14}}$) docked with DNA gyrase.

Compounds	Free energy of binding (ΔG) kcal/mol	Docking energy kcal/mol	Ki (inhibition constant) μM
A-1	−7.09	−7.49	6.37
A-2	−6.77	−7.52	10.84
A-3	−7.04	−8.01	1.24
A-4	−8.19	−9.07	992.57
A-5	−7.31	−7.81	4.36
A-6	−8.88	−9.72	310.99
A-7	−7.22	−8.36	5.12
A-8	−8.05	−8.79	11.91
A-9	−6.62	−7.40	5.96
A-10	−7.75	−8.45	2.29
A-11	−7.09	−8.12	2.37
A-12	−7.56	−8.34	2.88
A-13	−7.23	−8.08	2.79
A-14	−8.00	−8.88	30.98
Ciprofloxacin	−6.33	−7.19	23.10
Chloramphenicol	−4.20	−6.44	15.66

2.1.2. Molecular descriptors

(1) Octanol–water partition coefficient (log*P*).
(2) Bioconcentraion Factor (BCF).
(3) Polar surface Area (PSA).

Regarding a correlation of the steric parameters with activity, all chalcones of both set were found to correlate directly with the activity. The octanol–water partition coefficient (log*P*) is representative of steric interactions and in the present study it showed a good correlation with the bactericidal action of chalcones. A direct correlation of the activity with log*P* was indicative of the fact that chalcones with a higher log*P* are expected to be more active as is reflected in the activity of halogenated chalcones (Table 1).

The bromo and chloro groups' containing compounds ($\mathbf{A_4}$, $\mathbf{A_6}$, $\mathbf{A_9}$, and $\mathbf{A_{10}}$) are more active ones in the series of 14 compounds (Table 3). Their Log*P* values (6.42, 6.24, 614, and 6.00, respectively) are higher than the other compounds. As stated earlier in this discussion that the position of substitutent groups also affects the activity of the compounds e.g. $\mathbf{A_2}$ (2-bromo) is less active (Log*P* = 5.83) than $\mathbf{A_4}$ (5-bromo) (Log*P* = 6.42. This difference is caused by steric difference in both molecules. Experimental and theoretical data indicates that the halogen group is somewhat more active against bacteria than methyl group. This difference can be attributed to the hydrophobic property that bromo is more hydrophobic than chloro and in turn it has greater binding energy to bind with biomolecule and inhibit their life cycle and growth.

2.2. Docking studies

The docking experiments were performed using the bacterial DNA gyrase structure with newly synthesized quinoline based

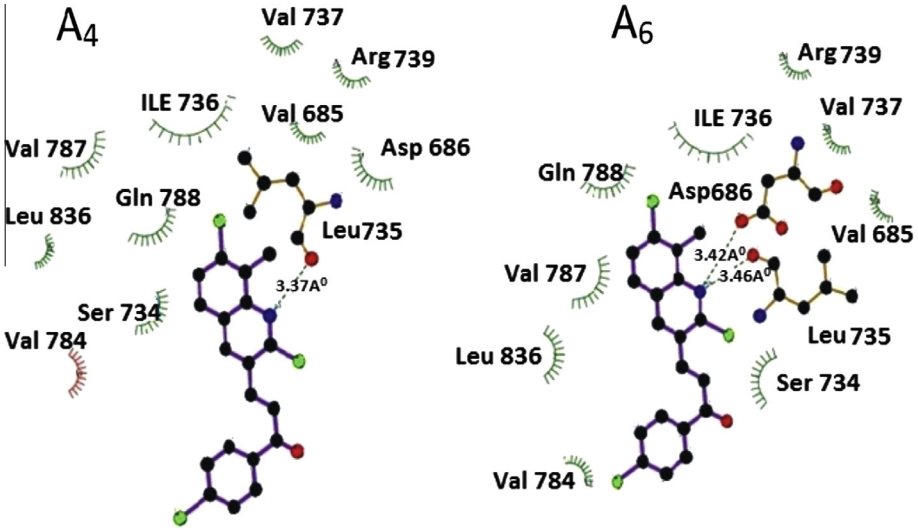


Fig. 3. Predicted binding conformations of chalcones $\mathbf{A_4}$ and $\mathbf{A_6}$ with catalytic portion of DNA gyrase.

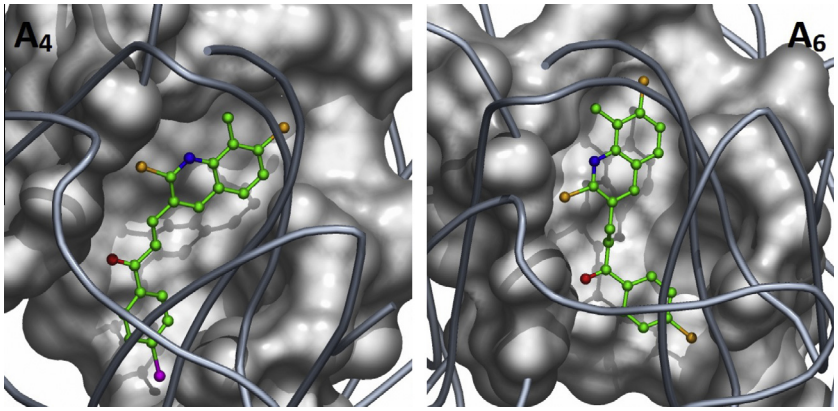


Fig. 4. Docking model derived for $\mathbf{A_4}$ and $\mathbf{A_6}$ with the catalytic portion of DNA gyrase.

chalcones (**A_1–A_{14}**) and with reference compounds (Ciprofloxacin and Chloramphenicol). The DNA gyryase structure was obtained from RCSB Portein data base (PDB ID 1Zi0). DNA gyrase is a unique type II topoisomerase which is responsible for the surper-coiling activity of DNA in bacteria. We used the AutoDock to determine the docked energy, the free energy of binding (ΔG) and the inhibition constant Ki compared with experimental biological activity (Table 1 and Table 2). The calculated interaction energies for (**A_1–A_{14}**) are good in agreement with experimental result which shows that **A_4, A_6, A_8** and **A_{14}** are potent inhibitor of DNA gryase as compared to other chalcones and reference standard (Table 4). The chain residue of DNA gryase to which the most potent inhibitors **A_4, A_6, A_8** and **A_{14}** binds are LEU735, GLN788, ASP686, SER734, VAL737, VAL787, ARG739, VAL685, LEU836 and VAL784 as shown in (Figs. 3 and 4).

The close contact of quinoline ring of **A_4** and **A_6** with ILE736, VAL737 and VAL787 residue (3.85, 3.69 and 3.62 Å) suggested hydrophobic interaction. The nitrogen of quinoline make interaction through hydrogen bonding with ASP686 and LEU735 residue (3.42 and 3.46 Å respectively). On the other hand –Cl of pyridine ring make interaction with VAL737 and GLN788 residue (3.37 and 3.20 Å respectively). The Br group on para position of benzene also interact with VAl 784 (3.07) and the Cl group on para position of benzene interact with VAL784 and LEU836 (3.40 and 3.59 Å respectively). These interactions stabilized the most potent compound **A_4** and **A_6** in the active site of DNA gyrase as contributing favorable free binding energy (ΔG −8.19 and −8.88 kcal/mol respectively).

Fig. 4 predict the 3D model of DNA gyrase complexed with compounds **A_4** and **A_6** occupies the same space which shows a great affinity with DNA gyrase. The result of the docking experiment support the postulation that compounds **A_4** and **A_6** may act as potent inhibitor of the DNA gyrase. These theoretical results were also supported by the experimental data (Table 2).

Spectral data: Spectral data (IR, ^{1}H NMR and MS) of all the newly synthesized compounds were found in good agreement with the proposed structures. IR spectra of the compounds **A_1–A_{14}** showed an absorption band at 1659 cm^{-1}, typical of the stretching vibrations of chalcone moiety. No peaks were found due to starting material aldehydic functionality as impurity. In the ^{1}H NMR spectra of the chalcones two very sharp doublets were found around δ 7.61–7.63 ppm for H_α and δ 8.17–8.13 ppm for H_β with *J*-value 15–16 Hz for the *trans* chalcones. The molecular ion observed in the mass spectra for all the chalcones confirmed their molecular masses. The base peak, in the mass spectra of most of the chalcones, was obtained possibly by the cleavage of Ar–Cl bond. While in bromo and chloro substituted chalcones the base peak is due to the cleavage of two bonds i.e. CO-phenyl and phenyl-Cl/Br bonds.

3. Conclusions and outlook

It is concluded from the above discussion that the chalcones (**A_4, A_5, A_6, A_8,** and **A_{10}**) are comparatively more active than (**A_1, A_2, A_3, A_7, A_9, A_{11}, A_{12},** and **A_{13}**). We have divided these compounds into four categories for their antibacterial activities and represented in Table 1 *i.e.* IC_{50} = 0.125 mg/mL or below as significantly active, 0.5 mg/mL as good active, 1.0 mg/mL as moderately active and >1 mg/mL as low active. The compounds (**A_4, A_5, A_6, A_8 A_{10}** and **A_{14}**) are found potentially active antibacterial agents. The activity depends on the position of substituent, the hydrophobic effect of bromo group is greater at 4-position of benzene and thiophene as exhibited in **A_4** and **A_8**. On the other hand the hydrophobic effect of bromo group decreases at 2-position of benzene and thiophene as in **A_2**, **A_3** and **A_9** respectively**.** This is also supported by docking experiment, bioassay the calculated Log*P* values of studied Compounds. The docking experiment and bioassay tell us that compounds A_4 and A_6 are the most potent inhibitor of DNA gyrase.

Category	Compounds
Significant	**A_4, A_6, A_8**
Good	**A_5, A_{10} A_{14}**
Moderate	**A_1, A_2, A_3, A_7, A_9 A_{11}, A_{12}, A_{13}** and **A_{14}**

4. Experimental section

General: Melting points were taken on Gallenkamp melting point apparatus. IR spectra were recorded in KBr pellets on Perkin Elmer infrared spectrophotometer. ^{1}H NMR spectra were performed in $CDCl_3$ on Brücker/XWIN NMR (300 MHz) and TMS was used as internal standard (chemical shifts, δ in ppm) unless otherwise specified. Mass spectra were recorded on a Jeol MS Route instrument. Thin layer chromatography (TLC) was performed with aluminium sheets – Silica gel 60 F254 purchased from Merck. Purification of synthesized compounds was made by recrystallization from appropriate solvents. Reagent grade chemicals such as phosphoryl chloride, acetophenones, *N*,*N*-dimethylformamide (Sigma–Aldrich and Alfa Aesar) were used.

4.1. Bioassay conditions

4.1.1. Anti-bacterial activity

We have performed the anti-bacterial activity against *E. coli* (Gram-negative), *K. aerogenes* (Gram-negative), *S. typhimurium* (Gram-negative), *S. aureus* (Gram-positive), *S. pyogenes* (Gram-positive) and *B. subtilis* (Gram-positive). We have used MH medium (Mueller–Hinton medium) which composed of 1.5 g of beef extract, 1.7 g of starch and casein hydroxylate. All the stock solutions of new synthesized chalcones were prepared in DMSO. The stock solutions of new synthesized chalcones were used along with sterilized MH medium. The colorimetric method was used to determine the MIC (Minimum Inhibitory Concentration) values by using MMT dye.

4.2. Enzyme inhibition

We have been used the Blanche et al. [51] method for the purification of *S. aureus* DNA gyrase enzyme form the crude extract of *S. aureus*. The *S. aureus* was grown in a medium which was composed of 2 g of yeast extract, 1.2 g of $(NH_4)_2SO_4$, 8 g of Na_2HPO_4, 2 g of $K_2H_2PO_4$, 0.2 g of MgSO4, 4.0 g of glucose per liter of the distilled water. According to Blanche [51] the decatenation and supercoiling were performed.

4.2.1. Docking protocol

The docking studies were performed by using the autodock docking software. The structures of the studied compounds were drawn using ChemBio Ultra 11.0, then energies of all the compounds were minimized by using Gaussian 09 at B3LYP/6-31(d). The Gasteiger–Huckel method was used to assign the charges to the ligand. The DNA gyryase structure was obtained from RCSB Portein data base (PDB ID 1Zi0). In order to prepare the enzymes the hydrogens atoms were added at a P^H range of (6.5–8.1). By the aid of AutoDock tools the salvation parameters and kollman united atom type chargers were added (Morris, Goodsell et al., 1998). The autogrid program was used to generate the affibity (gird) maps of 20 × 20 × 20 Å gird points and 0.375 Å spacing. (Morris, Goodsell et al., 1998).

4.3. Methods of preparation of precursors for chalcones

4.3.1. N-acetylation of substituted aniline

0.1 mol of substituted aniline, 0.2 mol of glacial acetic acid was added in a 250 ml flask. To this mixture, catalytic amount of phosphoric acid was added and the mixture was refluxed for 5–6 h. After the completion of the reaction (by TLC monitoring), the mixture was poured in ice-cold water and stirred well. The crude product was precipitated out at once. These precipitates were filtered and washed with ice-cold water. The pure product was obtained by recrystallized from boiling water.

4.3.2. Synthesis of 2-chloro-3-formyl quinoline (Conventional Thermal Method)

Vilsmeier reagent was prepared by adding $POCl_3$ (107.4 g, 64.4 ml, 0.70 mol) dropwise in DMF (18.6 g, 19.2 ml, 0.25 mol) at 0 °C with constant stirring. To this solution acetanilide (0.10 mol) was added and the mixture was stirred for 15mins at room temperature. Then this mixture was stirred at 70–80 °C for 16 h. After the completion of reaction (TLC monitoring), the mixture was poured in ice-cold water (500 ml) and stirred vigorously (30 min at 0–10 °C). The 2-chloro-3-quinolinecarbaldehyde was precipitated out, which was filtered off and washed with water (200 ml), dried and recrystallized from ethanol.

*4.3.3. General method for the synthesis of quinolinyl chalcones (**A_1**–A_{14})*

A mixture of formylquinoline (1 mmol) and an aromatic ketone (1 mmol) in methanol (50 mL) was stirred at room temperature, followed by dropwise addition of aq. NaOH (4 mL, 10%). The stirring was continued for 2 h and the reaction mixture was then kept at 0 °C for 24 h. Subsequently, it was poured onto ice-cold water (200 mL). The precipitates were collected by filtration, washed with cold water followed by cold MeOH. The resulting chalcones were recrystallized from $CHCl_3$ and dried *in vacuo*.

4.3.3.1. (E)-3-(2,7-dichloro-8-methylquinolin-3-yl)-1-(3,4-dimetho xyphenyl)prop-2-en-1-one (A_1). Yield, 85%. M.p. **180–182** °C. IR (KBr, cm^{-1}): 1652 (C=O), 1596 (C=C), 1156 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.403** (1H, s, Ar—H), **8.152** (1H, d, J = 15.6 Hz, CH of olefinic bond), **7.698** (1H, dd, J_1 = 2 Hz, J_2 = 8.4 Hz, Ar—H), **7.63** (3H, m, CH of olefinic bond and Ar—H), **7.564** (IH, m, Ar—H), **6.939** (1H, d, J = 8.4 Hz, Ar—H), **3.972** (6H, s, OCH_3), **2.818** (3H, s, CH_3); Calc Mass 402.27 MS, **402.17** $[M+H]^+$ (Molecular ion Peak) **366.25** $[M+H]^+$ –Cl.

4.3.3.2. (E)-1-(2-bromophenyl)-3-(2,7-dichloro-8-methylquinolin-3-yl)prop-2-en-1-one (A_2). Yield, 78%. M.p. **198–200** °C. IR (KBr, cm^{-1}): 1659 (C=O), 1598 (C=C), 1152 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.139** (1H, s, Ar—H), **8.057** (2H, d, J = 7.6 Hz, CH of olefinic bond and Ar—H), **7.629** (2H, d, J = 8.8 Hz,CH of olefinic bond and Ar—H), **7.526** (3H, m, Ar—H), **7.24** (1H, s, Ar—H), **2.821** (3H, s, CH_3); Calc Mass **421.11** MS, **421.92** $[M+H]^+$ (Molecular ion Peak) **388.17** $[M+2+H]^+$ –Cl.

4.3.3.3. (E)-1-(3-bromophenyl)-3-(2,7-dichloro-8-methylquinolin-3-yl)prop-2-en-1-one (A_3). Yield, 80% white Color solid. M.p. **172–175** °C. IR (KBr, cm^{-1}): 1654 (C=O), 1591 (C=C), 1157 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.428** (1H, s, Ar—H), **8.180** (2H, m, CH of olefinic bond and Ar—H), **7.96** (1H, d, J = 7.6 Hz, Ar—H), **7.734** (1H, d, J = 8 Hz, Ar—H), **7.658** (1H, d, J = 8.4 Hz, Ar—H), **7.551** (2H, m, CH of olefinic bond and Ar—H), **7.406** (IH, t, J = 8 Hz Ar—H), **2.816** (3H, s, CH_3); Calc Mass **421.11** MS, **421.92** $[M+H]^+$ (Molecular ion Peak) **388.17** $[M+2+H]^+$ –Cl.

4.3.3.4. (E)-1-(4-bromophenyl)-3-(2,7-dichloro-8-methylquinolin-3-yl)prop-2-en-1-one (A_4). Yield, 84% white Color solid. M.p **185–188** °C. IR (KBr, cm^{-1}): 1651 (C=O), 1599 (C=C), 1153 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.408** (1H, s, Ar—H), **8.181** (1H, d, J = 16 Hz, CH of olefinic bond), **7.906** (2H, d, J = 8.8 Hz, Ar—H), **7.653** (3H, m, CH of olefinic bond and Ar—H), **7.558** (1H, m, Ar—H), **7.519** (IH, s, Ar—H), **2.814** (3H, s, CH_3); Calc Mass **421.11** MS, **421.92** $[M+H]^+$ (Molecular ion Peak) **388.17** $[M+2+H]^+$ –Cl.

4.3.3.5. (Z)-1-(2-bromo-4-methoxyphenyl)-3-(2,7-dichloro-8-methylquinolin-3-yl)prop-2-en-1-one (A_5). Yield, 84% white Color solid. M.p. **190–192** °C. IR (KBr, cm^{-1}): 1655 (C=O), 1593 (C=C), 1154 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.133** (1H, s, Ar—H), **8.048** (2H, d, J = 8.8 Hz, CH of olefin and Ar—H), **7.625** (1H, d, J = 8.8 Hz, CH of olefin), **7.554** (1H, d, J = 8.4 Hz, Ar—H), **7.240** (1H, s, Ar—H), **6.965** (2H, d, J = 8.8 Hz, Ar—H), **3.877** (3H, s, OCH_3), **2.821** (3H, s,CH_3); Calc Mass **451.14** MS, **451.08** $[M+H]^+$ (Molecular ion Peak) **415.58** $[M+H]^+$ –Cl.

4.3.3.6. (E)-1-(4-chlorophenyl)-3-(2,7-dichloro-8-methylquinolin-3-yl)prop-2-en-1-one (A_6). Yield, 75%. M.p. **168–170** °C. IR (KBr, cm^{-1}): 1650 (C=O), 1590 (C=C), 1150 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.410** (1H, s, Ar—H), **8.183** (1H, d, J = 15.6 Hz, CH of olefin), **7.987** (2H, d, J = 8.4 Hz, Ar—H), **7.645** (1H, d, J = 8.8 Hz, Ar—H), **7.530**(4H, m, CH of olefin and Ar—H), **2.818** (3H, s, CH_3); Calc Mass **376.66** MS, **376.00** $[M+H]^+$ (Molecular ion Peak) **340.00** $[M+H]^+$ –Cl.

4.3.3.7. (E)-3-(2,7-dichloro-8-methylquinolin-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (A_7). Yield, 70%. M.p **200–202** °C. IR (KBr, cm^{-1}): 1662 (C=O), 1594 (C=C), 1160 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.402** (1H, s, Ar—H), **8.153** (1H, d, J = 16 Hz, CH of olefin), **8.065** (2H, d, J = 1.6 Hz, Ar—H), **7.629** (2H,m, CH of olefin and Ar—H), **7.561** (1H, m, Ar—H), **6.995** (2H, d, J = 8.4 Hz, Ar—H), **3.893**(3H, s, OCH_3), **2.816** (3H, s, CH_3); Calc Mass **372.14** MS, **372.08** $[M+H]^+$ (Molecular ion Peak) **336.08** $[M+H]^+$ –Cl.

4.3.3.8. (E)-1-(5-bromothiophen-2-yl)-3-(2,7-dichloro-8-methylquinolin-3-yl)prop-2-en-1-one (A_8). Yield, 56%. M.p. **162** °C. IR (KBr, cm^{-1}): 1660 (C=O), 1592 (C=C), 1159 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.389** (1H, s, Ar—H), **8.209** (1H, d, J=15.6 Hz, CH of olefin), **7.633** (2H, m, Ar—H), **7.56** (1H, d, J=8.8 Hz, CH of thiazole), **7.393** (1H, d, J = 15.6 Hz, CH of olefin), **7.171** (1H,d, J = 4 Hz, CH of thiophene), **2.816** (3H, s, CH_3); Calc Mass **427.14** MS, **428.00** $[M+4+H]^+$ (Molecular ion Peak) **392.17** $[M+2+H]^+$ –Cl.

4.3.3.9. (E)-1-(3-bromothiophen-2-yl)-3-(2,7-dichloro-8-methylquinolin-3-yl)prop-2-en-1-one (A_9). Yield, 60%. M.p. **170** °C. IR (KBr, cm^{-1}): 1648 (C=O), 1593 (C=C), 1161 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.406** (1H, s, Ar—H), **8.22** (1H, d, J = 15.6 Hz, CH of olefin), **7.831** (1H, d, J = 15.6 Hz, CH of olefin), **7.657**(1H, d, J = 8.8 Hz, Ar—H), **7.575** (2H, m, CH of thiazole), **7.164** (1H, d, J = 8.8 Hz, Ar—H), **2.814** (3H, s, CH_3); Calc Mass **427.14** MS, **427.92** $[M+H]^+$ (Molecular ion Peak) **392.08** $[M+H]^+$ –Cl.

4.3.3.10. (E)-1-(5-chlorothiophen-3-yl)-3-(2,7-dichloro-8-methylquinolin-3-yl)prop-2-en-1-one (A_{10}). Yield, 53%. M.p. **148** °C. IR (KBr, cm^{-1}): 1656 (C=O), 1594 (C=C), 1158 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.383** (1H, s, Ar—H), **8.202** (1H, d, J = 15.6 Hz, CH of olefin), **7.747** (2H, m, Ar—H), **7.66**(1H, m, CH of olefin), **7.425** (1H, d, J = 10 Hz, CH of thiophene), **7.024** (1H, d, J = 4 Hz, CH of thiophene), **2.812** (3H, s, CH_3); Calc Mass **380.95** MS, **382.99** $[M+H]^+$ (Molecular ion Peak) **347.49** $[M+H]^+$ –Cl

4.3.3.11. (E)-3-(2,7-dichloro-8-methylquinolin-3-yl)-1-(2,5-dimethylthiophen-3-yl)prop-2-en-1-one (A_{11}). Yield, 60%. M.p. **158** °C. IR (KBr, cm^{-1}): 1658 (C=O), 1595 (C=C), 1157 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.353** (1H, s, Ar—H), **8.076** (1H, d, J = 15.6 Hz, CH of olefin), **7.627** (1H, d, J = 8.8 Hz, Ar—H), **7.542** (1H, d, J = 8.8 Hz, Ar—H), **7.339** (1H, d, J = 16 Hz, CH of olefin), **7.096** (1H, s, CH of thiophene), **2.811** (3H, s,CH_3), **2.721** (3H, s, CH_3), **2.442** (3H, s, CH_3); Calc Mass 376.30 MS, **376.17** $[M+H]^+$ (Molecular ion Peak) **340.17.08** $[M+H]^+$ –Cl.

4.3.3.12. (E)-3-(2,7-dichloro-8-methylquinolin-3-yl)-1-(4-methylthiophen-2-yl)prop-2-en-1-one(A_{12}). Yield, 50%. M.p. **140** °C. IR (KBr, cm^{-1}): 1654 (C=O), 1589 (C=C), 1149 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.395** (1H, s, Ar—H), **8.198** (1H, d, J = 15.6 Hz, CH of olefin), **7.707** (1H, s, CH of thiazole), **7.645** (1H, d, J = 8.8 Hz, Ar—H), **7.553** (1H, d, J = 8.8 Hz, Ar—H), **7.454** (1H, d, J = 15.6 Hz, CH of olefin), **7.315** (1H, s, CH of thiophene), **2.814** (3H, s, CH_3), **2.330** (3H, s, CH_3); Calc Mass **362.27** MS, **362.17** $[M+H]^+$ (Molecular ion Peak) **326.25** $[M+H]^+$ –Cl.

4.3.3.13. (E)-3-(2,7-dichloro-8-methylquinolin-3-yl)-1-(5-methylthiophen-2-yl)prop-2-en-1-one(A_{13}). Yield, 67%. M.p. **130** °C. IR (KBr, cm^{-1}): 1654 (C=O), 1598 (C=C), 1160 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.380** (1H, s, Ar—H), **8.172** (1H, d, J = 15.6 Hz, CH of olefin), **7.715** (1H, d, J = 4 Hz, CH of thiazole), **7.637** (1H, d, J = 8.8 Hz, Ar—H), **7.547** (1H, d, J = 8.8 Hz, Ar—H), **7.436** (1H, d, J = 15.6 Hz, CH of olefin), **6.868** (1H, d, J = 4 Hz, CH of thiophene), **2.811** (3H, s, CH_3), **2.572** (3H, s, CH_3); Calc Mass **362.27** MS, **362.11.08** $[M+H]^+$ (Molecular ion Peak) **364.11** $[M+H]^+$ –Cl.

4.3.3.14. (E)-3-(2,7-dichloro-8-methylquinolin-3-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)prop-2-en-1-one (A_{14}). Yield, 45%. M.p. **158–160 °C**. IR (KBr, cm^{-1}): 1658 (C=O), 1595 (C=C), 1156 (C=N of quinoline ring). ^1H NMR ($CDCl_3$) δ: **8.391** (1H, s, Ar—H), **8.147** (1H, d, J = 15.6 Hz, CH of olefin), **7.606** (4H, m, CH of olefin and Ar—H), **7.542** (1H, m, Ar—H), **6.961** (1H, d, J = 8.8 Hz, Ar—H), **4.319** (4H, dd, J_1 = 5.2 Hz, J_2 = 13.2 Hz, CH_2 of acetal), **2.811** (3H, s, CH_3); Calc Mass **400.25** MS, **400.17** $[M+H]^+$ (Molecular ion Peak) **364.17** $[M+H]^+$ –Cl.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bioorg.2014.03.006. These data include MOL files and InChiKeys of the most important compounds described in this article.

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