International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 4 Issue 6 ǁ June 2015 ǁ PP.53-76

Synthesis of (3-(2-Chloroquinolin-3-yl)Oxiran-2-yl)(Phenyl)Methanone Derivatives and *in vitro* and *in silico* Study of Their Various Biological Activities

N Preveena[1], Gopalpur Nagendrappa[1*], TH Suresha Kumara[2], Amit Kumar Tiwari[1], MS Chaithanya[3], GS Nagananda[4], PS Sujan Ganapathy[5], Tayur N Guru Row[6], Amar A Hosamani[6], PR Chethana[7]

[1]*P.G. Department Of Chemistry, Jain University, 52 Bellary Road, Hebbal Campus, Bangalore - 560024, India*
[2]*Department Of Chemistry, UBDT College Of Engg. (A Constituent College Of VTU, Belagavi), Davanagere-577 004, Karnataka, India*
[3]*Department Of Pharmaceutical Chemistry, Sri Siddaganga College Of Pharmacy, Tumkur,India*
[4]*Centre For Emerging Technologies, Jain Global Campus, Kanakapura Taluk, India*
[5]*Centre For Advanced Studies In Biosciences, Jain University, 52 Bellary Road, Hebbal Campus, Bangalore - 560024, India*
[6]*Solid State And Structural Chemistry Unit, Indian Institute Of Science, Bangalore, India*
[7]*Department Of Chemistry, Bangalore University, Bangalore, India*
**corresponding author: Email: gnagendrappa@gmail.com, Tel.:+91 9945784334*

ABSTRACT:*(3-(2-chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanones were prepared, under very mild conditions, from 2-chloroquinoline-3-carbaldehyde by Darzens reaction, and were characterized by spectral and X-ray analysis. They were studied for their pharmacological properties both by in vitro and in silico procedures, which included free radical scavenging activity, antibacterial activity, fungal susceptibility, brine shrimp toxicity and DNA cleavage, and computation of oral rat LD_{50} values, compliance of Lipinski's Rule of Five, bioactivity using Molinspiration program and molecular docking on Glucosamine-6-phosphate synthase (Glc-N-6-P synthase). They show very good antioxidant, antibacterial and antifungal activities. One of the compounds (***5***) was found to have much better antifungal activity than the standard Fluconazole. Their toxicity was determined by using brine shrimps. The LC_{50} values indicate that several of the compounds are more toxic to the test organism than the anticancer drug Etoposide used as standard. The in silico studies include computation of oral rat LD_{50} values by four different methods, drug likeness and bioactivity on the basis of compliance of Lipinski's Rule of Five and physical properties, and molecular docking with GlcN-6-P synthase. The results of in silico studies corroborate the findings of in vitro experiments. DNA cleavage studies indicated that the compounds are ineffective as cleavage agents. Taking all the results together, it is quite evident that quinolinyl epoxy ketones have highly promising pharmacological properties and have the potential to be developed into therapeutically beneficial products.*

Keywords:*(3-(2-Chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanones • Chloroquinolinyl aroyl epoxides • Darzens reaction • Antioxidant activity • Antimicrobial activity • Brine shrimp toxicity • Drug-likeness • Molecular docking studies*

I. INTRODUCTION

2-Chloroquinoline-3-carbaldehyde and its substituted products are remarkably versatile intermediates for synthesizing a variety of compounds containing quinoline unit, which find many pharmaceutical and other applications. The aldehydic and the chloro functional groups in chloroquinoline carbaldehyde molecule serve as convenient handle to steer these synthons to prepare a range of useful products. In addition, the popularity of these chloroquinoline carbaldehydes as synthons may also be attributed to the ease of their preparation from substituted acetanilides by Vilsmeier-Haack reaction [1]. The interest in quinoline compounds is traceable to the fact that most of them show pharmacological properties [2] and many of the important drugs are quinoline derivatives [3]. Drug resistance among pathogens due to widespread and indiscriminate use of antibiotics [4] has prompted renewed efforts to search for novel antimicrobial agents and since quinoline compounds have the potential to act as inhibitor of antibiotic efflux pumps in cells [3d], the possibility of these compounds being developed into drugs that can overcome antibiotic resistance is quite promising.

Darzens condensation, a reaction between α-halo-ketones or α-haloesters and aldehydes, is a powerful procedure for formation of carbon-carbon bond with a simultaneous generation of epoxy function group next to the keto or ester function, and considerable innovative work is reported in recent time [5]. Although 2-chloroquinoline-3-carbaldehydes have served as readily available synthons for a variety of new quinoline products [1, 2c, 2f] it has not been exploited for Darzens condensation, except one report [6] that describes the synthesis of a few quinolinyl epoxy ketones under stronger conditions and much longer duration, but delivering very modest yields of products. Since many quinoline compounds are pharmacologically active, we expect that quinolinyl epoxy ketones could possess effective pharmacological properties.

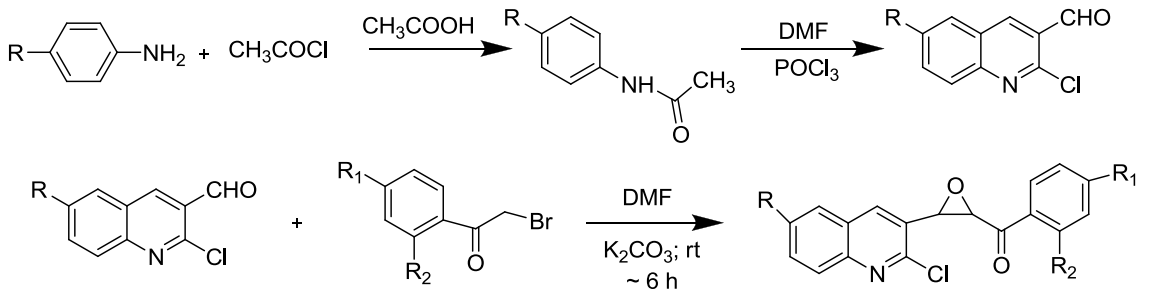
With these facts as background, we synthesized several quinolinyl epoxy ketones, namely (3-(2-chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanone (**1**) and quinoline and phenyl ring substituted derivatives (**2-11**) under very mild conditions and made fairly comprehensive preliminary *in vitro* as well as *in silico* studies of their pharmacological properties, such as antioxidant activity, toxicity, antimicrobial activity, DNA cleaving property, drug-likeness and molecular docking aspects. We found that all the quinolinyl epoxy ketones that we have studied exhibited excellent biological properties, with a few of them showing good potential to be developed into compounds of medicinal value, and wish to report the results here.

II. RESULTS AND DISCUSSION

2.1. Preparation of the quinolinyl epoxy ketones 1-11

For the present study, we have synthesized the parent epoxide (3-(2-chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanone (**1**) and ten of its substituted derivatives (**2-11**) by Darzens reaction of 2-chloroquinoline-3-carbaldehydes and its 6-substituted derivatives with phenacyl bromide and its 2- and 4-mono- and 2,4-disubstituted derivatives. The required 2-chloroquinoline-3-carbaldehydes were prepared from acetanilide and its 4-substituted derivatives using Vilsmeier-Haack procedure. The synthetic route is presented in **Scheme 1**.

Scheme 1



1. R = R_1 = R_2 = H
2. R = CH_3 ; R_1 = R_2 = H
3. R = OCH_3; R_1 = R_2 = H
4. R = H, R_1 = R_2 = Cl
5. R = CH_3 ; R_1 = R_2 = Cl
6. R = OCH_3; R_1 = R_2 = Cl
7. R = R_2 = H; R_1 = CH_3
8. R = R_1 = CH_3; R_2 = H
9. R =OCH_3; R_1 = CH_3; R_2 = H
10. R = R_1 = R_2 = Cl
11. R = Cl; R_1 = CH_3; R_2 = H

For Darzens condensation we have used a very mild base, K_2CO_3, as catalyst and carried out the reaction at room temperature for just 6 hours. The yields of the epoxides **1-11** (mixtures of *cis* and *trans* isomers) obtained are excellent (**Table 1**). A previous report [6] mentions using more than 100 equivalents of the strong alkaline aq. KOH solution as catalyst in toluene and running the reaction for more than 24 h that gave modest yield (55%) of epoxides **1** and **2**. (The epoxides **3-11** that we have prepared are new and are not reported earlier). In the present reaction procedure a far less quantity (just about 1/4th eq.) of very mild base (K_2CO_3) is used, and the reaction takes just about 6 h for completion and delivers excellent yields of epoxy ketones. The products **1, 2, 4-7, 10** and **11** were predominantly *trans* epoxides mixed with small quantities of the corresponding *cis* isomers and were easily purified by column chromatography. However, **3**, **8** and **9** were mixtures of *cis* and *trans* epoxides in almost equal amounts and we did not quite succeed in separating the two isomers. The products were identified by their IR, NMR and HRMS data. It was possible to select single crystals of pure

trans-**1**, *cis*-**3** and *cis*-**8**, and obtain their X-ray crystal structures. We have reported here the X-ray structures of *trans*-**1** (**Fig 1**) and *cis*-**3** (**Fig 2**).

2.2. Evaluation of different biological properties

In order to understand the potential drug-like properties of the synthesized compounds, we used *trans* isomers of **1**, **2**, **4**-**7**, **10** and **11** and *cis*-*trans* mixtures of **3**, **8** and **9** for in vitro biological tests, which included free radical scavenging activity, antibacterial activity, fungal susceptibility, brine shrimp toxicity and DNA cleavage. The *in silico* studies were conducted on *cis*- and *trans*-isomers of all the 11 epoxides. They included calculation of compliance of Lipinski's Rule of Five, oral rat LD_{50} values, bioactivity using Molinspiration program and docking on GlcN-6-P synthase using Autodock V3.0 program. All these studies together have clearly indicated that quinolinyl epoxy ketones **1**-**11** have good potential to be developed into therapeutically useful compounds. Discussion of the results obtained from bioactivity measurements follows.

2.2.1. Antioxidant activity measurement

All the quinolinyl epoxy ketones **1**-**11** were tested for their capacity to scavenge DPPH and ABTS free radicals employing established procedures [8, 9] and ascorbic acid was used as standard scavenging agent for comparison. The results are presented in **Table 2** and in graphical form in **Fig 3** and **Fig 4**. The results show that the test compounds **1**-**11** possess good free radical scavenging property, though their ability to scavenge DPPH radicals markedly differs from that of ABTS free radicals, both in order and degree, the latter being more effectively scavenged. An important outcome of these tests is that the compound **11** is found to be better (lowest LD_{50} value) than the standard used (ascorbic acid) and that **9** is as good as the standard in their effectiveness as ABTS radical scavenging agents. In the case of DPPH, the best scavenging efficiency is shown by the compound **7**, which is, however less than that of ascorbic acid.

Correlating the scavenging activity of **1**-**11** with their structures does not seem to be easy, because none of them has a functional group such as –OH or –NH- that contains active hydrogen, which is considered as essential for abstraction by DPPH or ABTS free radical. However, we speculate that the benzylic hydrogen of the $–CH_3$ group of p-tolyl moiety in **8**, **9** and **11** is likely to be abstracted particularly because of the C=O group in the para-position, as these compounds show the best scavenging activity towards ABTS free radicals. In the case of the remaining compounds, other mechanism such as abstraction of a π-electron from the aromatic ring (quinoline/benzene), could possibly be taking place. Anyway, irrespective of the kind of scavenging mechanism, the quinolinyl epoxy ketones **1**-**11**are evidently good free radical scavengers and they can interact with reactive oxygen species (ROS).

2.2.2. Antimicrobial activity

Antimicrobial activity was studied using the Gram positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis* and Gram negative bacterium *Escherichia coli*, and the fungi *Aspergillus niger* and *Aspergillus flavus*. Antibacterial activity of our compounds was compared with that of the antibiotics ofloxacin and ampicillin as standard, and fluconazole was used as standard in the measurement of antifungal activity. The activity was evaluated in terms of zones of inhibition and also minimum inhibition concentration, and the values are given in **Table 3** and **Table 4**. The results reveal that nine of the tested compounds possess reasonably good antibacterial and antifungal activity, while the compounds **3** (against *B. subtilis*)**, 4** (against *E. coli*) and **5** (against *S. aureus*) exhibit excellent antibacterial activity which is comparable with that of the standard antibiotics. It is noteworthy that **4** is more effective against *E. coli* than the standard. The same two compounds (**4** and **5**) also show the best antifungal activity that is similar to that observed for the standard compound fluconazole.

2.2.3. Evaluation of toxicity

Brine shrimp nauplii were used as test organisms for *in vitro* toxicity measurements. The toxicity profiles of the eleven quinolinyl epoxy ketones **1**-**11** were calculated from the percentage of brine shrimp mortality and are given in **Table 5**. For comparison the cytotoxic drug etoposide was used as standard. The LC_{50} values (µg/mL) indiacate that compound **3** is most toxic to the test organism *A. salina*, and it is followed by **11**, **8** and **10** in that order of their toxicity. All four compounds (**3**, **8**, **10** and**11**) are found to be far more cytotoxic than the standard drug etoposide. The least toxic one is compound **5**, which is followed by **4**. If we compare these results with the antimicrobial activity values, we can notice an interesting point, which is that while **4** and **5** are least effective in terms of toxicity the same two compounds are the most effective antimicrobial agents. This mutually exclusive property could be potentially useful while considering these compounds for developing as medicinal products. It should also be noted that seven of the eleven compounds are more toxic to the test organism than the standard drug etoposide. The toxicity values obtained by different in silico procedures (**Table 7**) are not comparable with those obtained from *in vitro* method (**Table 5**), because the values from the former methods do not concur within themselves and differ widely, and secondly, perhaps because the test organisms used for *in vitro* experiments and considered for *in silico* calculations are different. However, the results from all

the methods very clearly show that several of the eleven tested compounds are more toxic than the standard drugs used in the respective methods, which means that the compounds have the potential to test further for suitability in medicinal applications.

2.2.4. Computational evaluation of drug-likeness and bioactivity

The results from all our *in vitro* bioactivity measurements indicate that the quinolinyl epoxy ketones **1-11** used in these experiments indicate that they have good potential to be considered for pharmacological applications. This conclusion is further supported by computation of various physical properties (**Table 8**) and bioactivity (**Table 9**) of these compounds using Molinspiration software programme. The calculations were carried out for *cis* and *trans* isomers separately. The results were essentially the same for both, and show that seven of them comply with Lipinski's rule of five, while the other four exhibit only one violation which is perfectly acceptable even in the case of drugs in use. The bioactivity values computed for our compounds are similar to those calculated for ofloxacin, ampicillin (antibacterial drugs), and fluconazole (antifungal drug) which were used as standard models. These various computational data undoubtedly indicate that the compounds **1-11** possess drug-like properties.

2.2.5. DNA cleavage studies

In order to understand the possible interaction of our compounds with the basic building blocks of life, we undertook to study in vitro their cleaving effect on cPU DNA. Experiments for these cleavage studies were carried out using compounds **1** and **2.** The results showed that the two compounds have no DNA cleaving property (**Table 6, Fig 5**). Because the results were negative, we did not extend the cleavage study to other compounds.

2.2.6. Molecular docking studies

The docking parameters such as binding energy, docking energy, intermolecular energy, number of H-bonds, inhibitory constant and bonding sites, have been computed separately for *cis* and *trans* isomeric epoxides. The results of these studies (**Table 10** and **11; Fig 6, 7** and **8**) indicate good interaction of our compounds with the enzyme GlcN-6-P synthase which plays important role in cancer, diabetes and fungal diseases [20]. For computational simulation of binding of the test compounds, they were docked to the enzyme to get the best conformer, from which we obtained the binding energy, docking energy and the number of hydrogen bonds formed.

The docking of the compounds **1-11** (*cis* and *trans*) with GlcN-6-P synthase domain reveal that they interact with one or the other amino acid in the active pockets as shown in **Fig 6** and **7**. The topology of the active sites of the enzyme lined by interacting amino acids, as indicated in the ligplot (**Fig 8**), was similar in the tested molecules.

Considering the binding energies of the compounds in **Table 10** and **11**, it is evident that the *trans* isomers bind to the enzyme better than the *cis* isomers. Another notable difference between the *cis* and *trans* isomers is the number of H-bonds, with *trans* compounds having more H-bond interactions. It is also clear that all the 22 compounds have lower binding energy than the drug ampicillin and several of them (trans-**1**, **2**, **3**, **5**, **8**, **9** and **10**, and cis-**3**, **4**, **6**, and **7**) are better than the antifungal drug fluconazole. Comparing the results of *in vitro* bioactivity studies with the results of docking studies, we can observe some reasonably good agreement between the two, and it is interesting to note that *trans*-**5** which has good *in vitro* antibacterial properties is found to have the strongest features of binding with the enzyme.

III. EXPERIMENTAL

3.1. Synthesis of the quinolinyl epoxy ketones

3.1.1. Materials and methods

Chemicals were obtained from Sigma-Aldrich and SD Fine Chemicals companies and were purified when needed or used without further purification. Melting points were determined by open capillary method. Proton and carbon-13 NMR spectra were recorded on 400 MHz Bruker FT-NMR using TMS as the internal standard and $CDCl_3$ or DMSO-d_6 as solvent, and the chemical shifts (δ) are given in parts per million (ppm). The IR spectra (in KBr pellets) were recorded on a Shimadzu CVT-04 spectrophotometer. Merck silica gel 60 F254 TLC plates were used to monitor the progress of reactions and purity of products. The compounds were purified by chromatography on silica gel column using petroleum ether-ethyl acetate mixture (96:4 ratio) as eluant. 2-Chloroquinoline-3-carbaldehydes were synthesized from the corresponding acetanilides by Vilsmeier-Haack reaction following the literature procedure [1e]. Same reaction conditions were used for the synthesis of all quinolinyl epoxy ketones (**1-11**) used in this study and the typical procedure is given below.

3.1.2. Preparation of compounds

To a suspension of 1.0 g (5.2 mmol) of 2-chloroquinoline-3-carbaldehyde in DMF (4 mL), 1.25 g (6.25 mmol) of phenacyl bromide and 0.20 g (1.45 mmol) of K_2CO_3 were added. The reaction mixture was stirred at room temperature for about 6 h, the progress of the reaction being monitored by periodically testing the mixture by TLC. At the end of the reaction, the mixture was added to crushed ice, the precipitated product was collected by filtration and purified by column chromatography on silica gel using petroleum ether-ethyl acetate mixture (96:4 ratio) as eluting solvent, to obtain 1.40 g (87%) of 3-(2-chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanone (**1**).

Following the same procedure the other quinolinyl epoxy ketones **2-11** were prepared in excellent yield. The products **1**, **2**, **4-7**, **10** and **11** were predominantly *trans* with small amounts of *cis*, while remaining ones (**3**, **8** and **9**) were obtained as mixtures of their respective *cis* and *trans* isomers, as shown by the proton and carbon-13 NMR spectra of the crude products. We could obtain pure *trans*-**1**, **2**, **4-7**, **10** and **11** through column chromatography, but we were unsuccessful in separating **3**, **8** and **9**. The compounds were identified by their IR, ^1H and ^{13}C spectral and HRMS data. Single crystal X-ray analysis was carried out for two representative compounds, namely *trans*-**1** and *cis*-**3**. The yields, melting points and the IR absorption frequency values (C=O and epoxide) of the compounds **1-11** are provided in **Table 1**. We used pure trans-**1**, **2**, **4-7**, **10** and **11**, and mixtures of *cis* and *trans*-**3**, **8** and **9** for in vitro biological studies. Molecular modeling analyses were performed on the *cis* and *trans* isomer sets separately.

Table 1. Yield, melting points and IR (CO and epoxy bands) values of the quinolinyl epoxy ketones 1-11

Compound	R	R_1	R_2	mp (˚C)	Yield (%)	IR (cm^{-1})	
						Carbonyl band	epoxy band
1	H	H	H	138-140	87	1685	831
2	CH_3	H	H	175	90	1683	830
3	OCH_3	H	H	173-175	91	1684	833
4	H	Cl	Cl	148-150	81	1683	824
5	CH_3	Cl	Cl	145-147	83	1694	824
6	OCH_3	Cl	Cl	195-197	86	1709	827
7	H	CH_3	H	160-162	94	1682	836
8	CH_3	CH_3	H	164	88	1676	824
9	OCH_3	CH_3	H	158	88	1678	830
10	Cl	Cl	Cl	193-194	68	-	-
11	Cl	CH_3	H	186	63	1677	825

3.1.3. Spectral and HRMS data

3-(2-Chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanone (**1**) (*trans*)

Yellow solid; ^1H NMR (400 MHz, DMSO d_6): δ = 4.44 (d, J = 1.6 Hz, 1H), 4.92 (d, J = 2 Hz, 1H), 7.61 (t, 2H), 7.73(m, 2H), 7.87 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.16 (m, 3H), 8.45(s, 1H); ^{13}C NMR (400 MHz, DMSO d_6): δ = 56.63, 59.38, 127.24, 128.09, 128.18, 128.80, 128.92, 129.48, 131.73, 134.82, 135.48, 136.42, 147.10, 148.82, 192.96. IR (KBr, cm^{-1}): ν_{max} 1685.24,1 227.7, 1041.47, 1005.81, 831.48; HRMS (ESI) m/z Calcd for $C_{18}H_{12}ClNO_2Na^+$ $[M + Na]^+$, 332.0557; Found, 332.0454.

3-(2-Chloro-6-methylquinolin-3-yl)oxiran-2-yl)(phenyl)methanone (**2**) (*trans*)

Yellow solid; ^1H NMR (400 MHz, DMSO d_6): δ = 2.48 (s, 3H), 4.42 (d, J = 2.28 Hz, 1H), 4.51 (d, J = 2.52 Hz, 1H), 7.64 (m, 3H), 7.84 (m, 5H), 8.23 (s, 1H); ^{13}C NMR (400 MHz, DMSO d_6): δ = 21.57, 57.00, 61.50, 127.15, 127.42, 127.82, 128.13, 128.27, 130.57, 132.07, 132.55, 133.93, 134.71, 135.63, 137.92, 137.96, 145.73, 147.79, 194.99. IR (KBr, cm^{-1}): ν_{max} 1682.81, 1594.73, 1227.73, 1048.98, 1008.7, 829.94. HRMS (ESI) m/z Calcd for $C_{19}H_{14}ClNO_2Na^+$ $[M + Na]^+$, 346.0713; Found, 346.0611.

3-(2-Chloro-6-methoxyquinolin-3-yl)oxiran-2-yl)(phenyl)methanone (**3**) (*cis* + *trans*)

Yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3H), 4.22(d, J = 2 Hz, 1H), 4.47(dd, J = 0.8, 0.8 Hz, 1H), 4.78 (d, J = 4.8 Hz, 1H), 4.84 (dd, J = 0.4, 0.4 Hz, 1H), 7.11 (t, J = 2.8, 4 Hz, 1H), 7.32 (dd, J = 2.8, 2.8 Hz, 1H), 7.35 (m, 2H), 7.53 (m, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.9 (m, 2H), 8.08 (m, 1H), 8.19(s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 55.64, 55.70, 56.44, 56.68, 60.31, 60.40, 105.27, 105.59, 123.72, 123.80, 124.81, 127.76, 128.19, 128.35, 128.46, 128.58, 128.76, 128.82, 128.99, 129.46, 129.82, 133.93, 134.11, 134.26,

135.07, 135.29, 136.61, 143.31, 143.52, 145.66, 145.95,158.40, 158.62, 190.95, 192.22. IR (KBr, cm^{-1}): ν_{max} 1684.26, 1595.07, 1224.51, 1044.64, 1015.31, 833.06; HRMS (ESI) m/z Calcd for $C_{19}H_{14}ClNO_3Na^+$ $[M + Na]^+$, 362.0662; Found, 362.0560.

3-(2-Chloroquinolin-3-yl)oxiran-2-yl)(2,4-dichlorophenyl)methanone (**4**) (*trans*)
White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.09 (d, J = 2 Hz, 1H), 4.52 (m, 1H), 7.39 (dd, J = 2, 2 Hz, 1H), 7.49 (d, J = 2Hz, 1H), 7.60 (m, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.77 (m, 1H), 7.85 (m, 1H), 8.04 (m, 1H), 8.14 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 57.21, 62.44, 126.95, 127.71, 127.77, 127.83, 127.87, 128.50, 130.57, 131.19, 131.24, 133.38, 134.48, 135.03, 139.19, 147.55, 148.62, 194.16. IR (KBr, cm^{-1}): ν_{max} 1682.8, 1579.55, 1211.23, 1039.7, 1006.3, 823.85; HRMS (ESI) m/z Calcd for $C_{18}H_{10}C_{l3}NO_2Na^+$ $[M + Na]^+$, 399.9777; Found, 399.9675.

3-(2-Chloro-6-methylquinolin-3-yl)oxiran-2-yl)(2,4-dichlorophenyl)methanone (**5**) (*trans*)
White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3H), 4.07 (d, J = 1.6 Hz, 1H), 4.50 (d, J = 1.6 Hz, 1H), 7.39 (dd, J = 2, 2 Hz, 1H), 7.48 (d, J = 2 Hz, 1H), 7.59 (m, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H), 8.04 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.62, 57.28, 62.45, 126.66, 127.00, 127.69, 127.75, 128.12, 130.57, 131.22, 133.39, 133.45, 134.34, 134.49, 137.87, 139.15, 146.15, 194.23. IR (KBr, cm^{-1}): ν_{max} 1694.03, 1577.68, 1221.81, 1042.59, 1002.69, 823.5; HRMS (ESI) m/z Calcd for $C_{19}H_{12}C_{l3}NO_2Na^+$ $[M + Na]^+$, 413.9934; Found, 413.9831.

3-(2-Chloro-6-methoxyquinolin-3-yl)oxiran-2-yl)(2,4-dichlorophenyl)methanone (**6**) (*trans*)
White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3H), 4.07 (d, J = 2 Hz, 1H), 4.50 (dd, J = 0.4, 0.4 Hz, 1H), 7.08 (d, J = 2.8 Hz, 1H), 7.39 (m, 2H), 7.48 (d, J = 2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 9.6 Hz, 1H), 8.03 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 55.69, 57.29, 62.44, 105.26, 123.90, 127.75, 127.96, 128.14, 129.84, 130.57, 131.24, 133.39, 133.66, 134.48, 139.17, 143.57, 145.96, 158.63, 194.19. IR (KBr, cm^{-1}): ν_{max} 1709.9, 1581.75, 1215.5, 1041.2, 1003.3, 826.72; HRMS (ESI) m/z Calcd for $C_{19}H_{12}C_{l3}NO_3Na^+$ $[M + Na]^+$, 429.9883.

3-(2-Chloroquinolin-3-yl)oxiran-2-yl)(p-tolyl)methanone (**7**) (*trans*)
Pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 4.23 (d, J = 2 Hz, 1H), 4.46 (m , 1H), 7.29 (m, 2H), 7.60 (m, 1H), 7.76 (m,1H), 7.85 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H) , 8.03 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.84, 56.49, 60.28, 126.98, 127.66, 127.83, 128.29, 128.43, 128.53, 128.59, 128.65, 128.67, 129.49, 129.68, 131.05, 132.83, 135.22, 145.42, 147.45, 148.64, 191.61. IR (KBr, cm^{-1}): ν_{max} 1682.38, 1607.75, 1230.98, 1066.9, 1036, 761; HRMS (ESI) m/z Calcd for $C_{19}H_{14}ClNO_2Na^+$ $[M + Na]^+$, 346.0713; Found, 346.0611.

3-(2-Chloro-6-methylquinolin-3-yl)oxiran-2-yl)(p-tolyl)methanone (**8**) (*cis* + *trans*)
Pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 2.55 (s, 3H), 4.20 (d, J = 2 Hz, 1H), 4.45 (m, 1H), 4.75 (d, J = 4.4 Hz, 1H), 4.82 (dd, J = 0.8, 0.4 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 7.5 (dd, J = 2, 1.6 Hz, 1H), 7.60 (m, 3H), 7.80 (m, 3H), 7.96 (m, 3H), 8.12 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.55, 21.63, 21.75, 21.84, 56.31, 56.59, 60.29, 60.33, 124.65, 126.64, 126.67, 127.06, 127.13, 127.74, 128.09, 128.31, 128.44, 128.59, 128.77, 129.38, 129.48, 129.68, 132.62, 132.86, 133.12, 133.33, 134.57, 137.22, 137.47, 137.81, 145.18, 145.40, 145.86, 146.09, 147.41, 147.73, 190.34, 191.61. IR (KBr, cm^{-1}): ν_{max} 1675.65, 1599.79, 1236.78, 1047.78, 1007.75, 823.91; HRMS (ESI) m/z Calcd for $C_{20}H_{16}ClNO_2Na^+$ $[M + Na]^+$, 360.0870; Found, 360.0767.

3-(2-Chloro-6-methoxyquinolin-3-yl)oxiran-2-yl)(p-tolyl)methanone (**9**) (*cis* + *trans*)
Pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 1H), 2.36 (s, 1H), 2.44 (s, 3H), 3.91 (s, 1H), 3.94 (s, 3H), 4.20 (d, J = 2 Hz, 1H), 4.45 (m, 1H), 4.75 (d, J = 4.8 Hz, 1H), 4.82 (dd, J = 0.8, 0.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 7.21 (m, 1H), 7.31 (m, 2H), 7.41 (dd, J = 2.8, 2.8 Hz, 1H), 7.80 (m, 1H), 7.96 (m, 3H), 8.10 (s,1H), 8.18 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.76, 21.84, 55.63, 55.71, 56.32, 56.60, 60.33, 105.28, 105.61,123.68, 123.77, 124.93, 128.21, 128.31, 128.59, 128.72, 129.45, 129.51, 129.68, 129.82, 132.61, 132.85, 132.93, 136.55, 143.51, 145.42, 146.00, 158.62, 191.68. IR (KBr, cm^{-1}): ν_{max} 1678.24, 1498.9, 1223.56, 1045.66, 1025.94, 829.91; HRMS (ESI) m/z, Calcd for $C_{20}H_{16}ClNO_3Na^+$ $[M + Na]^+$, 376.0819; Found, 376.0716.

3-(2,6-Dichloroquinolin-3-yl)(2,4-dichlorophenyl)oxiran-2-yl)methanone (**10**) (*trans*)
Brownish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.08 (d, J = 2Hz, 1H), 4.51 (m ,1H), 7.4 (dd, J = 2, 2 Hz, 1H), 7.49 (d, J = 2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 2.4, 2.4 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 8.06 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 57.01, 62.36, 126.50, 127.56, 127.81, 129.07, 130.04, 130.58, 131.28, 132.11, 133.37, 133.64, 134.03, 134.41, 139.29, 145.86, 148.91, 193.95. HRMS (ESI) m/z, Calcd for $C_{18}H_9Cl_4NO_2Na^+$ $[M + Na]^+$, 433.9787.

3-(2,6-Dichloroquinolin-3-yl)oxiran-2-yl)(p-tolyl)methanone (**11**) (*trans*)
White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 4.20 (d, J = 2 Hz, 1H), 4.46 (m, 1H), 7.32 (d, J = 8 Hz, 2H), 7.71 (dd, J = 2, 2.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.98 (m, 3H), 8.13 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.85, 56.33, 60.20, 126.50, 127.63, 128.30, 128.60, 129.72, 129.81, 130.03, 132.00, 132.78, 133.60, 134.26, 136.98, 145.54, 145.81, 148.97, 191.40. IR (KBr, cm^{-1}): ν_{max} 1677.3, 1590.6, 1236.5, 1040.82, 1008.17, 825.4; HRMS (ESI) m/z, Calcd for $C_{19}H_{13}Cl_2NO_2Na^+$ $[M + Na]^+$, 380.0323; Found, 380.0221.

3.1.4. X-Ray crystal structure of *trans*-1 and *cis*-3

Crystals were grown from solvent evaporation method using ethyl acetate solvent at room temperature. A suitable single crystal of compound was carefully selected under a polarizing microscope and the single crystal data were collected on a Bruker Kappa Apex2 CCD diffractometer at 293(2) K. The X-ray generator was operated at 40 kV and 30 mA using Mo Kα(λ = 0.71073 A˚) radiation. Data were collected with ω scan width of 0.5°.The data reduction followed by Empirical absorption corrections were applied with the various modules within the Apex2 software suite [7a]. The structures were solved by direct methods using the SHELXTL package and refined by full-matrix least-squares on F^2 from the same [7b]. All Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined with a riding model. Structure was drawn using Mercury 3.1 [7c]. ORTEP diagrams of *trans*-**1** and *cis*-**3** are given in **Fig 1** and **Fig 2** respectively.

Crystal data for **1**: $C_{18}H_{12}ClNO_2$ (M =309.74 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 13.798(3) Å, b = 9.715(2) Å, c = 11.070(3) Å, β = 97.677(8)°, V = 1470.7(6) $Å^3$, Z = 4, T = 298 K, μ(MoKα) = 0.266 mm^{-1}, Dcalc = 1.399 g/cm^3, 18569 reflections measured (2.98° ≤ 2Θ ≤ 50°), 2591 unique (R_{int} = 0.0586, R_{sigma} = 0.0352) which were used in all calculations. The final R_1 was 0.0378 (>2sigma(I)) and wR_2 was 0.1024 (all data).

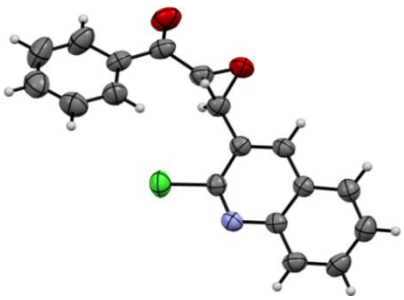


Figure 1 (*trans*-**1**)

Crystal data for **3**: $C_{19}H_{14}ClNO_3$ (M =339.76 g/mol): triclinic, space group P-1 (no. 2), a = 5.7986(15) Å, b = 11.220(3) Å, c = 12.203(3) Å, α = 85.549(12)°, β = 87.986(11)°, γ = 85.571(12)°, V = 788.8(4) $Å^3$, Z = 2, T = 296.15 K, μ(MoKα) = 0.259 mm^{-1}, Dcalc = 1.430 g/cm^3, 11280 reflections measured (3.34° ≤ 2Θ ≤ 50°), 2761 unique (R_{int} = 0.0602, R_{sigma} = 0.0399) which were used in all calculations. The final R_1 was 0.0716 (>2sigma(I)) and wR_2 was 0.2216 (all data).

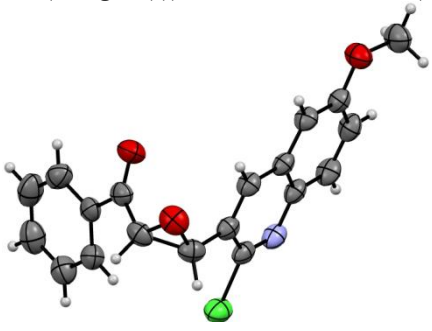


Figure 2 (*cis*-**3**)

3.2. Antioxidant activity measurement

3.2.1. Preparation of test solution

A solution of 10 mg of each compound in 10 mL of methanol was prepared. From each one of these solutions 10 µL, 20 µL, 30 µL, 40 µL and 50 µL equivalent to 10 µg, 20 µg, 30 µg, 40 µg and 50 µg respectively were pipetted out and each one was made up to 100 µL with methanol which provided test solutions varying in concentration from 10-50 µg/mL.

3.2.2. DPPH radical scavenging experiment [8]

Methanolic solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) of 0.1 mM concentration was prepared, and 5 mL of this solution was added to each of the sample solutions. The mixtures were shaken vigorously and allowed to stand at 27 ˚C for 20 minutes, after which their light absorbance was measured at 517 nm. Blank absorbance was measured with pure methanol and the DPPH solution as control. Each experiment was performed in triplicate. The radical scavenging activity of the tested compound was expressed as the inhibition percentage of free radical by the sample and was calculated using the following formula.

DPPH radical scavenging activity (%) = [(Control OD – Sample OD)/Control OD)] x 100.

3.2.3. ABTS radical cation decolourization assay [9, 10c]

2,2-Azinobis(3-ethylbenzothiozoline-6-sulfonic acid) cation radical ($ABTS^{+\cdot}$) was produced by reacting ABTS (7.0 mM) with ammonium persulfate (2.45 mM) for 12-16 h before use. Solutions of test compounds at concentrations ranging from 10-50 µg/mL were made up to 500 µL with DMSO and to each one of these 300 µL of ABTS solution was added, the final volume was being made up to 1.0 mL with ethanol. The solutions were allowed to stand in dark at room temperature for 30 min. The absorbance was read at 745 nm with DMSO as blank. Each experiment was performed thrice. The radical cation decolourization activity was expressed as inhibition percentage of cations by the sample and was calculated using the following formula.

ABTS radical scavenging activity (%) = [(Control OD – Sample OD)/Control OD)] x 100.

The results of the observation are presented in **Table 2**, and in graphical form in **Fig 3** and **Fig 4**.

Table 2. Scavenging activity and IC_{50} values of quinolinyl epoxy ketones

Compounds	Scavenging (%)		IC_{50} µg/mL	
	DPPH	ABTS	DPPH	ABTS
1	6.6120^{b}	12.0260^{d}	1585.12^{j}	163.33^{e}
2	7.0000^{b}	7.0340^{f}	839.79^{c}	229.47^{h}
3	7.3380^{b}	9.5640^{e}	1466.43^{h}	481.28^{l}
4	$6.5300^{b,c}$	11.5680^{d}	902.89^{d}	196.80^{f}
5	6.6180^{b}	9.5920^{e}	1103.96^{f}	260.50^{i}
6	6.7980^{b}	12.3120^{d}	1535.29^{i}	313.15^{j}
7	$6.4740^{b,c}$	8.7780^{e}	766.48^{b}	449.77^{k}
8	$6.3280^{b,c}$	15.9320^{c}	3083.98^{l}	110.00^{d}
9	6.6540^{b}	31.2260^{b}	2609.76^{k}	58.34^{c}
10	6.5222^{b}	11.3120^{d}	917.67^{e}	198.99^{g}
11	5.5960^{c}	30.4920^{b}	1413.30^{g}	48.93^{a}
Ascorbic acid (std)	32.09^{a}	52.082^{a}	49.73^{a}	55.66^{b}

Note: All values are mean of 15 replications for each sample. Mean values denoted by superscripts a-l differ significantly at $P < 0.01$ by Tukey (HSD) test.

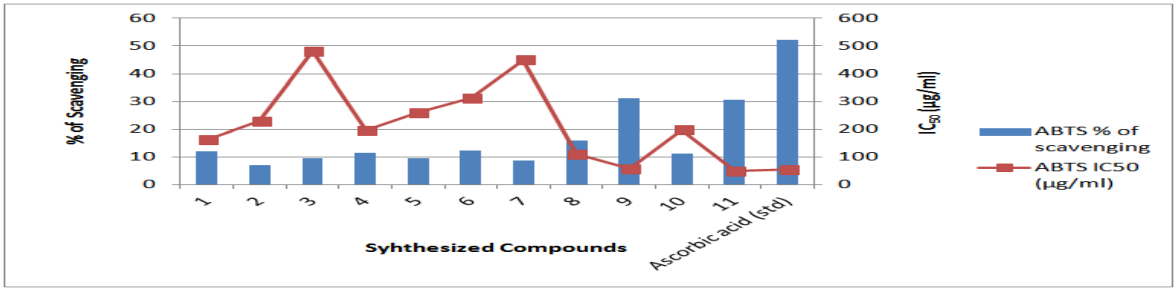


Figure 3. ABTS scavenging activity of different compounds and its IC_{50} (µg/mL)

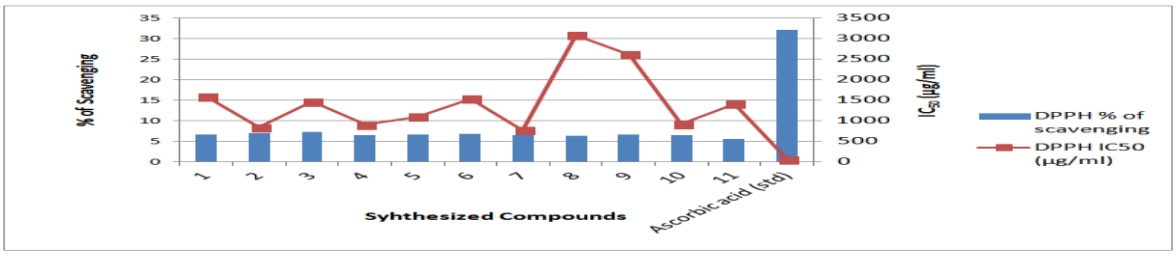


Figure 4. DPPH scavenging activity of different compounds and its IC_{50} (µg/mL

3.3. Antimicrobial activity measurement

3.3.1. Bacterial susceptibility test

The activity against Gram negative and Gram positive bacteria were tested using the agar well diffusion method [11, 2f]. Nutrient agar, purchased from HiMedia, India, was used as bacteriological medium. The test compounds were dissolved in 10% aqueous dimethylsulfoxide (DMSO) to a final concentration of 100 µg/100 µL. Pure DMSO was taken as negative control and 100 µg/100 µL solutions in 10% aqueous DMSO of ofloxacin and ampicillin were taken as the positive controls. Inoculum (100 µL) was aseptically introduced on to the surface of sterile agar plates and sterilized cotton swabs were used for the even distribution of the inoculum. Wells were prepared in the agar plates using a sterile cork borer of 6.0 mm diameter. Solutions (100 µL) of test and control compounds were introduced in the well. The same procedure was used for all the strains. The plates were incubated aerobically at 35 ˚C and examined after 24 h [12]. The diameter of the zone of inhibition produced by each test sample was measured and compared with those of commercial antibiotics ofloxacin and ampicillin. Minimum inhibitory concentration of synthesized compounds and the standard antibiotics was determined between 10 µg/10 µL - 100 µg/100 µL by well diffusion method for the bacteria that showed zone of inhibition.

3.3.2. Fungal susceptibility test

The antifungal activity of the title compounds was tested using agar well diffusion method. The potato dextrose agar plates were inoculated with 10 days old cultures of *Aspergillus niger* and *Aspergillus flavus* by point inoculation. A well of about 6.0 mm diameter with sterile cock borer was aseptically punched on each agar plate. The test compounds, each of 100 µg/100 µL concentration, were introduced into the well. A negative control well was prepared with 100 µL of pure DMSO and a positive control well of 100 µg/100 µL of fluconazole was also prepared. The plates were kept in laminar flow for 30 minutes for pre-diffusion of compounds to occur followed by incubation at 28 ˚C for 48 h. The resulting zones of inhibition were measured (in mm) using HiMedia zone scale [13]. Minimum inhibitory concentration of synthesized compounds and standard antifungal compounds was determined between 10 µg/10 µL - 100 µg/100 µL by well diffusion method for the fungi that showed zone of inhibition.

The results of bacterial and fungal susceptibility tests are given in **Table 3** and **Table 4.**

Table 3. Antimicrobial activity of quinolinyl epoxy ketones 1-11.

Compounds	Bacterial strains			Fungal strains	
	S. aureus	*B. subtillis*	*E. coli*	*A. niger*	*A. flavus*
Ofloxacin	18 ± 0.58	20 ± 0.58	20 ± 0.58		
Ampicillin	22 ± 0.58	20 ± 0.58	15 ± 0.58		
Fluconazole				25 ± 0.58	25 ± 0.58
1	12 ± 0.58*	12 ± 0.58	13 ± 0.58**	10 ± 0.58	10 ± 0.58
2	12 ± 0.58*	10 ± 0.58	12 ± 0.58	15 ± 0.58	15 ± 0.58
3	15 ± 0.58	15 ± 0.58*	14 ± 0.58**	12 ± 0.58	13 ± 0.58
4	10 ± 0.58**	13 ± 0.58**	18 ± 0.58	20 ± 0.58*	21 ± 0.58
5	15 ± 0.58	12 ± 0.58	15 ± 0.58*	21 ± 0.58*	20 ± 0.58*
6	12 ± 0.58*	12 ± 0.58	14 ± 0.58**	18 ± 0.58**	20 ± 0.58*
7	8 ± 0.58	10 ± 0.58	8 ± 0.58	10 ± 0.58	10 ± 0.58
8	12 ± 0.58*	10 ± 0.58	10 ± 0.58	12 ± 0.58	12 ± 0.58
9	8 ± 0.58	10 ± 0.58	8 ± 0.58**	10 ± 0.58	10 ± 0.58
10	14 ± 0.58	8 ± 0.58	15 ± 0.58	18 ± 0.58	18 ± 0.58
11	12 ± 0.58	12 ± 0.58	13 ± 0.58	18 ± 0.58	18 ± 0.58

The zone of inhibition values in mm are the mean of three experiments ± S.E.

* P<0.005 compared to standard. **P≤0.001 compared to standard.

Table 4. Minimun Inhibitory Concentration values in µg/mL for the epoxy ketones 1-11 and the standards used.

Compounds	Bacterial strains			Fungal strains	
	S. aureus	*B. subtillis*	*E. coli*	*A. niger*	*A. flavus*
Ofloxacin	14	8	18	-	-
Ampicillin	6	16	8	-	-
Fluconazole	-	-	-	8	8
1	100	100	100	100	100
2	24	24	24	12	24
3	24	24	24	24	24
4	24	10	20	10	10
5	14	14	14	10	10
6	50	50	50	10	10
7	100	100	100	100	100
8	100	100	100	100	100
9	100	100	100	100	100
10	50	50	50	18	18
11	100	100	100	14	14

3.4. Toxicity studies

3.4.1. Materials

The cytotoxocity drug etoposide (Etopa^{TM}), batch number GEA12-02, a semi-synthetic derivative of podophyllotoxin, was purchased from Getwell Oncology Pvt Limited and used as standard.
O.S.I.Pro 80 *Artemia salina* cysts (100% brine shrimp eggs) were purchased from Pet Food Accessories, Hyderabad, India, and used for obtaining the test organisms (brine shrimp larvae, nauplii) for the toxicology studies [10].

3.4.2. Culture and harvesting of the nauplii

A. salina cysts were stored at -4 ˚C before use. They were incubated for hatching in a shallow rectangular jar (14 cm x 9 cm x 5 cm) filled with 250 mL of a 3.3% solution of artificial sea water. A perforated plastic divider with 2 mm diameter holes was clamped into the jar to make two compartments of unequal sizes. The cysts and yeast were sprinkled into the larger compartment which was darkened by covering. The smaller compartment was illuminated by a tungsten filament lamp and gently purged with air and was incubated at 28 ˚C under controlled condition. After 48 hours, *A. salina* cysts hatched to give nauplii [10]. The phototropic nauplii, which had moved to the illuminated side of the jar, were collected by pipette.

3.4.3. Preparation of solutions of compounds and standard

The synthesized compounds and the standard anti-cancer drug etoposide (1.0 mg each) were taken in vials, 200 µL of DMSO was added, the mixtures were sonicated to get clear solutions which were then made up to 1000 µL with distilled water.

3.4.4. Bioassay of *A. salina*

For toxicity tests, *A. salina* nauplii were placed in test plates using a Pasteur pipette. The volume was adjusted to 5 mL by sea water. A drop of dry yeast suspension (3 mg in 5 mL of artificial sea water) was added as food to each plate. From the stock solutions of compounds 500 µL, 50 µL and 5 µL which corresponded to 500, 50 and 5 µg/mL respectively were transferred to plates. Incubation under illumination was done at 25-28 ˚C for 24 hours. The numbers of surviving nauplii were counted and compared with numbers in the plates containing only solvent and reference cytotoxic drug (etoposide). The nauplii counting was done with the aid of a 3-times magnifying glass and the percentage of deaths at the three dose levels was determined. However, in cases where deaths in the control jars were detected, the percentage of mortality (% M) was calculated as follows.
% M = % of survival in the control - % of survival in the test compound plate.
The LC_{50} was determined by using regression equation. LC_{50} is the measure of toxicity level of test compound to *A. salina* nauplii. The results are presented in **Table 5**.

Table 5. Toxicological study of quinolinyl epoxy ketones 1-11 and anti-cancer drug etoposide on *Artemia salina* nauplii

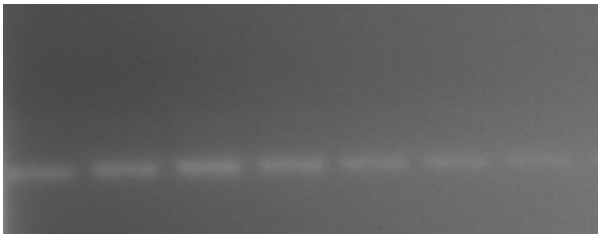
Compounds	% survival in solution of			LC_{50} (µg/mL)	LC_{50} (ppm)
	5 µg/mL	50 µg/mL	500 µg/mL		
1	100	50	40	462.19	462.72
2	100	80	30	339.96	340.34
3	50	45	30	26.45	26.48
4	80	65	55	612.53	613.23
5	65	55	50	879.66	880.67
6	85	50	40	316.95	317.31
7	45	25	5	193.31	193.53
8	50	40	25	83.011	83.1
9	60	55	40	229.62	229.88
10	70	40	20	99.59	99.7
11	60	35	35	37.03	37.07
Etoposide	90	60	40	356.15	356.55

Compounds	% mortality in solution of			LC_{50} (µg/mL)	LC_{50} (ppm)
	5 µg/mL	50 µg/mL	500 µg/mL		
1	0	50	60	462.19	462.72
2	0	20	70	339.96	340.34
3	50	55	70	26.45	26.48
4	20	35	45	612.53	613.23
5	35	45	50	879.66	880.67
6	15	50	60	316.95	317.31
7	55	75	95	193.31	193.53
8	50	60	75	83.011	83.1
9	40	45	60	229.62	229.88
10	30	60	80	99.59	99.7
11	40	65	65	37.03	37.07
Etoposide	10	40	60	356.15	356.55

3.5. DNA cleavage studies

3.5.1. Method

Agarose gel electrophoresis procedure was employed to determine the extent of cleavage of supercoiled (SC) DNA in the presence of test compounds (**1** and **2**) and oxidizing agent hydrogen peroxide (H_2O_2) and reducing agent 3-mercaptopropionic acid (MPA). In a typical reaction, supercoiled pUC DNA (0.2 µg), taken in 50 mM Tris-HCl buffer (pH 7.2) containing 50 mM NaCl, was treated with the compounds. The extent of cleavage was measured from the intensities of the band using UVITEC Gel Documentation System. For mechanistic investigations, inhibition reactions were performed on adding the reagents prior to the addition of compounds. The solutions were incubated for 1 h in a dark chamber at 37 ˚C followed by addition to the loading buffer containing 25% bromophenol blue, 0.25% xylene cyanol and 30% glycerol (2 µL), and the solution was finally loaded on 0.8% agarose gel containing 1.0 µg/mL ethidium bromide (EB). Electrophoresis was carried out for 2 h at 60 V Tris-acetate-EDTA (TAE) buffer. Bands were visualized by UV light and photographed for analysis. Due corrections were made to the observed intensities for the low level of NC form present in the original sample of SC DNA and for the low affinity of EB binding to SC in comparison to nicked-circular (NC) and linear forms of DNA [14]. The results are presented in **Fig 5** and **Table 6**.



Lane No 1 2 3 4 5 6 7

Figure 5. Bands from DNA cleavage by quinolinyl epoxy ketones 1 and 2

Table 6. Selected cleavage data of SC pUC 19 by quinolinyl epoxy ketones 1 and 2

Lane No	Experiment	[complex] µM	Result
1	Control DNA	-	-
2	DNA + 1	60	No cleavage
3	DNA + 2	60	No cleavage
4	DNA + 1 + MPA	60	No cleavage
5	DNA + 2 + MPA	60	No cleavage
6	DNA + 1 + H_2O_2	60	No cleavage
7	DNA + 2 + H_2O_2	60	No cleavage

3.6. In silico toxicity studies [15]

The median lethal dose (LD_{50}) for the eleven compounds has been evaluated using four available rat oral QSAR LD_{50} models by using Toxicity Estimation Software Tool (T.E.S.T) version 4.1. The methodologies used were Consensus method, (which is the average of the predicted toxicities for other QSAR methodologies), Hierarchical Clustering method, FDA method and Nearest Neighbor method. The structures of the compounds were entered for *cis* and *trans* isomers separately through the use of text file containing SMILES (simplified molecular input line entry system) notations. The SMILES notation structures of *cis* and *trans* quinolinyl epoxide derivatives **1**-**11** differ slightly. However, the overall results of molecular modeling computations were the same for both sets of isomers, excluding in the case of molecular docking, where the *cis* and *trans* isomers showed perceptible differences in interaction points of contact with the target enzyme, GlcN-6-P synthase (See below). The oral rat LD_{50} values evaluated by the four computational methods are summarized in **Table 7**. The ID numbers of the compounds corresponding to each method and the predicted LD_{50} log 10 values (mol/kg) are not included for brevity.

Table 7. Batch predictions of Oral rat LD_{50} values (mg/kg) by four different methods

Compounds	Consensus method	Hierarchical method	FDA method	Nearest Neighbor method
1	2971.37	-	3033.12	2910.89
2	2702.85	-	2644.73	2762.25
3	2276.49	-	1787.80	2898.75
4	655.29	-	1477.90	290.55
5	731.40	1199.28	1082.74	301.32
6	1009.28	1046.79	3131.86	313.60
7	970.49	-	340.98	2762.25
8	1073.89	1346.43	3738.36	246.05
9	1698.44	1137.34	4956.14	869.19
10	782.37	-	1931.02	316.98
11	739.24	-	1987.99	274.89

Etoposide: 1784 mg/kg (experimental)

3.7. Drug likeness and bioactivity estimation [16]

Lipinski's rule of five is commonly employed for evaluation of a chemical compound for its drug-like properties, which can be predicted by in silico methods. For the purpose of calculating drug-likeness and bioactivity of our test compounds **1-11**, we have used the well known Molinspiration software program. The estimated physical properties to check compliance of Lipinski's rule of five are presented in **Table 8** and the estimated bioactivity values are provided in **Table 9**.

Table 8. Estimated physical properties and Lipinski's RO5 of the quinoline derivatives 1-11 by Molinspiration

Compounds	miLogP[a]	TPSA[b]	Natoms[c]	MW[d]	nON[e]	nOHNH[f]	nviol[g]	nrotb[h]	volume[i]
1	3.828	42.491	22	309.75	3	0	0	3	259.61
2	4.252	42.491	23	323.78	3	0	0	3	276.17
3	3.86	51.725	24	339.78	4	0	0	4	285.15
4	5.111	42.491	24	378.64	3	0	1	3	286.68
5	5.536	42.491	25	392.67	3	0	1	3	303.24
6	5.144	51.725	26	408.67	4	0	1	4	312.22
7	4.276	42.491	23	323.78	3	0	0	3	276.17
8	4.701	42.491	24	337.81	3	0	0	3	292.73
9	4.309	51.725	25	353.81	4	0	0	4	301.71
10	5.765	42.491	25	413.09	3	0	1	3	300.21
11	4.93	42.491	24	358.22	3	0	0	3	289.7
Ofloxacin	0.262	75.014	26	361.37	7	1	0	2	311.15
Ampicillin	-0.873	112.73	24	349.41	7	4	0	4	298.87
Flucanazole	-0.118	81.664	22	306.28	7	1	0	5	248.96

[a] Octanol-water partition coefficient. [b] Molecular polar surface area. [c] Number of non-hydrogen atoms. [d] Molecular weight. [e] Number of hydrogen bond acceptors (O and N atoms). [f] Number of hydrogen bond donors (OH and NH groups). [g] Number of Rule of 5 violations.
[h] Number of rotatable bonds. [i] Molecular volume.

Table 9. Bioactivity of compounds 1-11 calculated by Molinspiration

Compounds	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-0.04	0.02	-0.27	-0.26	-0.24	0.11
2	-0.08	-0.06	-0.30	-0.27	-0.27	0.03
3	-0.06	-0.06	-0.25	-0.21	-0.25	0.06
4	-0.08	0.04	-0.25	-0.18	-0.28	0.05
5	-0.13	-0.04	-0.29	-0.21	-0.33	-0.02
6	-0.11	-0.04	-0.25	-0.16	-0.32	0.01
7	-0.07	-0.06	-0.29	-0.27	-0.27	0.04
8	-0.07	-0.06	-0.28	-0.25	-0.24	0.03
9	-0.10	-0.13	-0.28	-0.23	-0.29	0.00
10	-0.08	0.03	-0.24	-0.17	-0.25	0.05
11	-0.07	-0.07	-0.29	-0.27	0.05	0.01
Ofloxacin	0.23	-0.14	-0.06	-0.13	-0.26	0.35
Ampicillin	0.04	-0.47	-0.71	-0.61	0.87	0.25
Fluconazole	0.04	0.01	-0.09	-0.23	-0.09	0.03

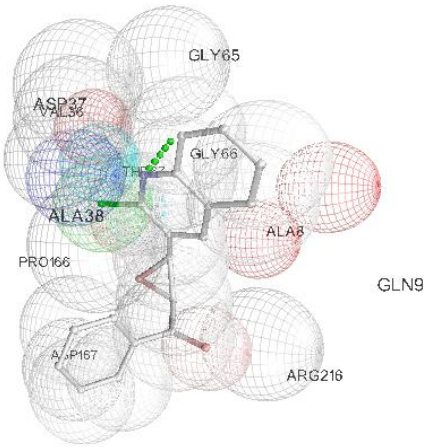
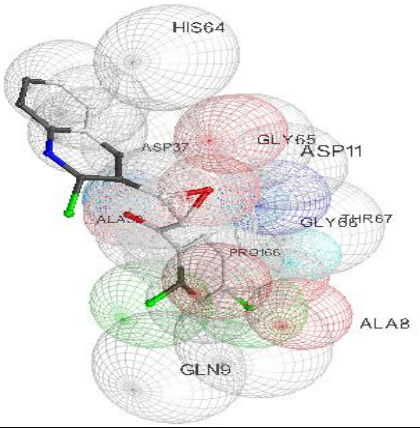
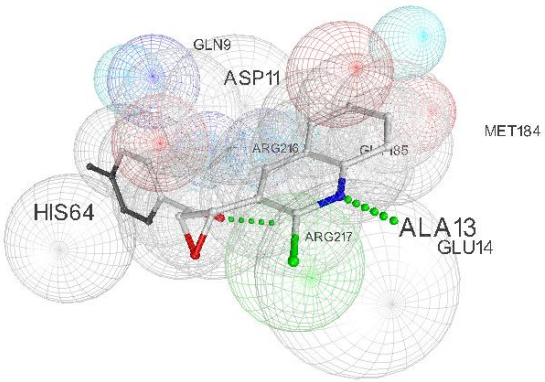
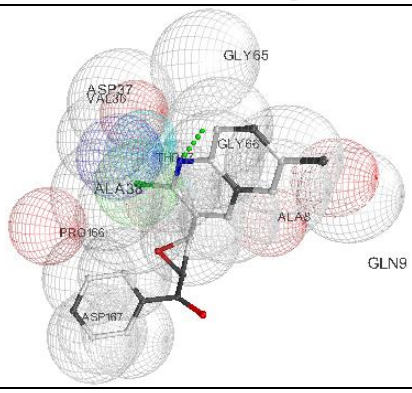
3.8. Molecular docking studies

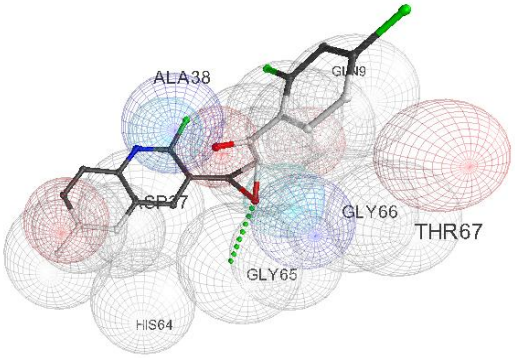
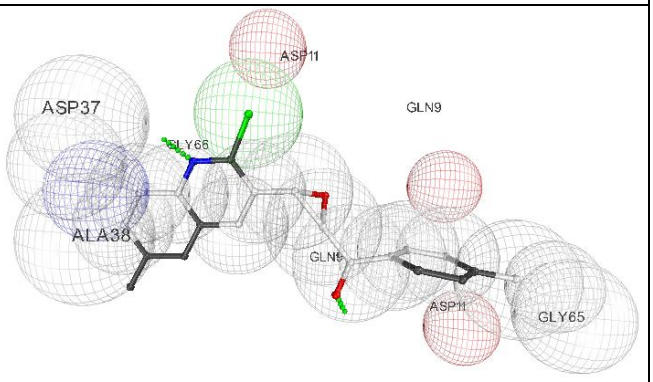
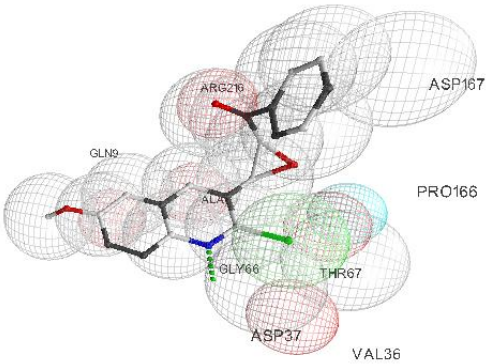
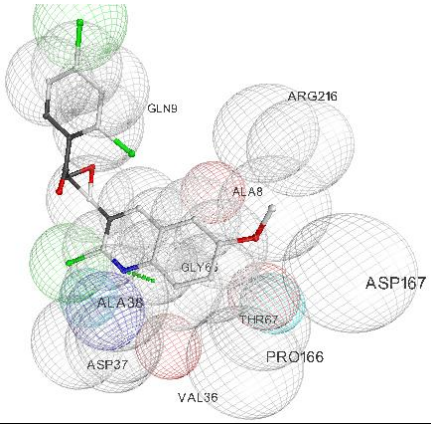
The three dimensional structure of target protein GlcN-6-P synthase having keyword 1XFF was downloaded from PDB (www.rcsb.org/pdb) structural database. This file was then opened in SPDB viewer edited by removing the heteroatoms, adding C terminal oxygen. The active pockets on target protein molecule were found out using CASTp server [17]. The ligands were drawn using ChemDraw Ultra 6.0 and assigned with

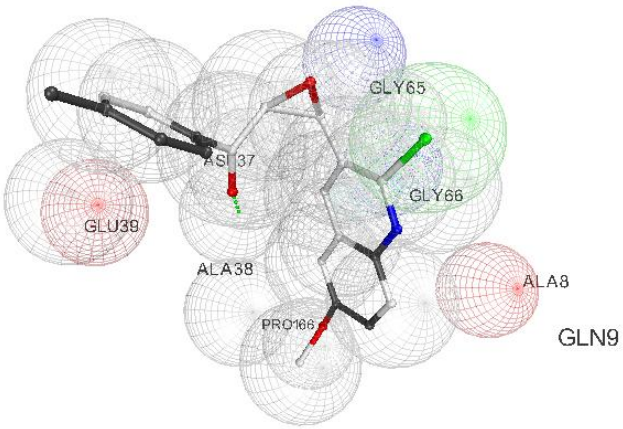
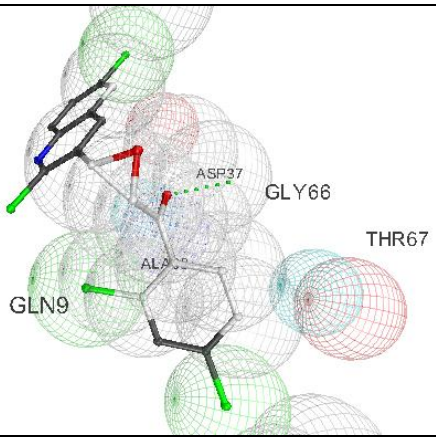
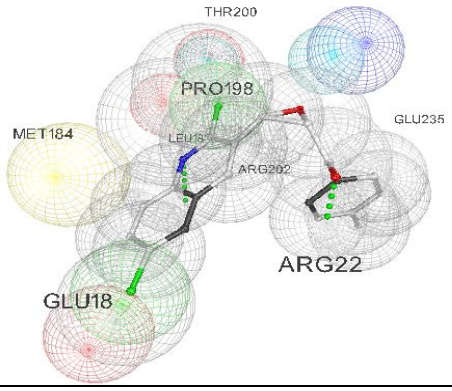
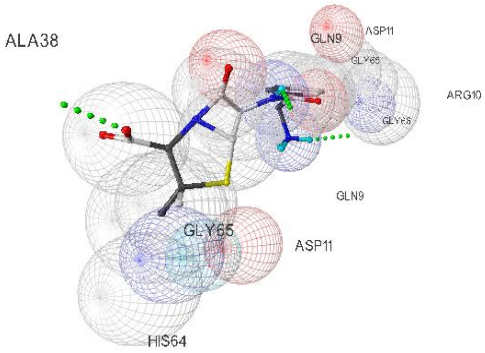
proper 2D orientation (ChemOffice package). Three dimensional coordinates were prepared using PRODRG server [18]. Autodock V3.0 was used to perform Automated Molecular Docking in AMD Athlon (TM)2x2 215 at 2.70 GHz, with 1.75 GB of RAM. AutoDock 3.0 was compiled and run under Microsoft Windows XP service pack 3. For docking, grid map is required in AutoDock, the size of the grid box was set at 126, 72 and 84 Å (R, G, and B), and grid center 1.807, 40.359, 0.01 for x, y, and z-coordinates. All torsions were allowed to rotate during docking. The Lamarckian genetic algorithm and the pseudo-Solis and Wets methods were applied for minimization, using default parameters [19]. The newly synthesized *cis* and *trans* **1-11,** totally 22 compounds, were taken as ligands and docked against target enzyme molecule, GlcN-6-P synthase.
The results of the studies are presented in **Table 10** and **11**, and in **Fig 6** and **7**.

Table 10. Molecular docking of *cis*-1 to *cis*-11 with glucosamine-6-phosphate synthase

Molecule	Binding energy	Docking energy	Inhibitory constant	Intermol energy	H-bonds	Bonding
1	-7.96	-9.44	1.45e-006	-8.9	1	1a::DRG:NAG:GPS:B:GLY66:HN
2	-7.76	-8.77	2.05e-006	-8.7	1	1b::DRG:OAN:GPS:B:ASP11:OD1
3	-8.35	-9.31	7.59e-007	-9.28	2	1c::DRG:NAG:GPS:A:GLU14:HN 1c::DRG:OAP:GPS:B:ARG217:HH22
4	-8.11	-9.45	1.13e-006	-9.04	1	2a::DRG:NAG:GPS:B:GLY66:HN
5	-7.96	-9.37	1.46e-006	-8.89	1	2b::DRG:OAN:GPS:A:ASP11:OD1
6	-8.04	-9.17	1.28e-006	-8.97	3	2c::DRG:OAN:GPS:B:GLN9:O 2c::DRG:OAP:GPS:B:GLN9:HE21 2c::DRG:NAG:GPS:B:GLY66:HN
7	-8.15	-9.68	1.06e-006	-9.4	2	3a::DRG:OAN:GPS:A:PRO166:O :GPS:A:THR67:OG1 3a::DRG:NAG:GPS:A:GLY66:HN
8	-6.98	-8.71	7.62e-006	-8.23	3	3b::DRG:OAN:GPS:A:GLN9:O 3b::DRG:OAY:GPS:A:THR67:OG1 3b::DRG:NAG:GPS:A:GLY66:HN
9	-6.51	-8.02	1.69e-005	-7.76	2	3c::DRG:NAG:GPS:B:GLN9:O 3c::DRG:OAP:GPS:B:ALA38:HN
10	-7.72	-8.9	2.19e-006	-8.65	2	5b::DRG:OAN:GPS:B:GLN9:O 5b::DRG:OAP:GPS:B:GLY66:HN
11	-7.63	-8.96	2.56e-006	-8.56	3	5c:DRG:OAN:GPS:B:GLU235:OE1 5c::DRG:OAP:GPS:A:ARG22:HH21 5c::DRG:NAG:GPS:B:ARG202:HH21
Ampicillin	-6.14	-7.05	3.16e-005	-7.38	3	Ampicillin::DRG:H:GPS:A:GLN9:O Ampicillin::DRG:HBP:GPS:B:GLN9:O Ampicillin::DRG:OAX:GPS:A:ALA38:HN
Flucanazole	-8.14	-7.69	1.07e-006	-9.7	5	Fluconazole::DRG:NAS,OAP:GPS:A:ARG201:H22 Fluconazole::DRG:NAU:GPS:B:THR200:HG1 Fluconazole::DRG:NAK:GPS:B:ARG202:HE Fluconazole::DRG:NAK:GPS:B:ARG202:HH21 Fluconazole::DRG:NAU:GPS:B:ARG201:HN

1	 GLY65 ASP37 VAL36 GLY66 ALA38 ALA8 PRO166 GLN9 ARG216
2	 HIS64 ASP37 GLY65 ASP11 PRO166 ALA8 GLN9
3	 GLN9 ASP11 MET184 ARG216 HIS64 ARG217 ALA13 GLU14
4	 GLY65 ASP37 VAL36 GLY66 ALA38 ALA8 PRO166 GLN9

5	 ALA38 GLN9 ASP37 GLY66 THR67 GLY65 HIS64
6	 ASP11 ASP37 GLN9 GLY65 ALA38 GLN9 ASP11 GLY65
7	 ARG216 ASP167 GLN9 PRO166 GLY66 THR67 ASP37 VAL36
8	 GLN9 ARG216 ALA8 ASP167 ALA38 THR67 PRO166 ASP37 VAL36

9	
10	
11	
Ampicillin	

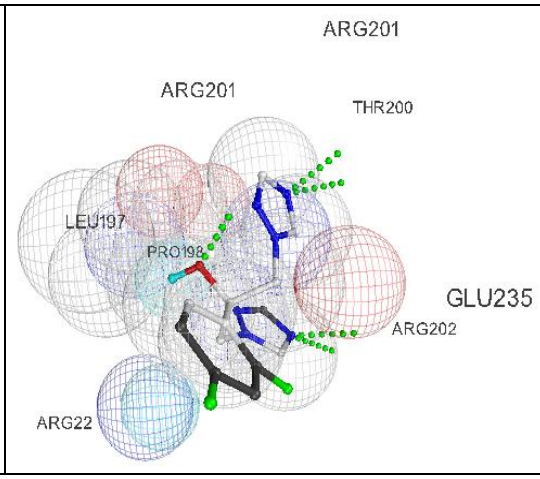
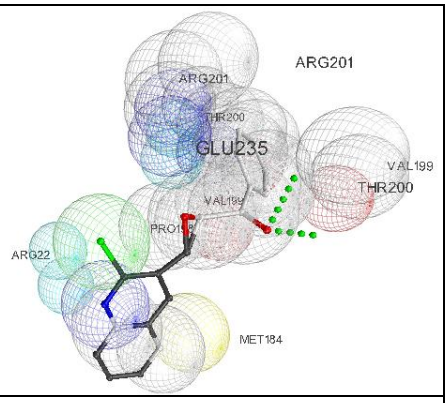
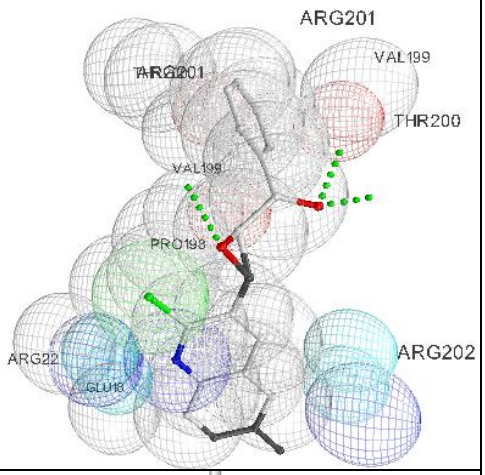
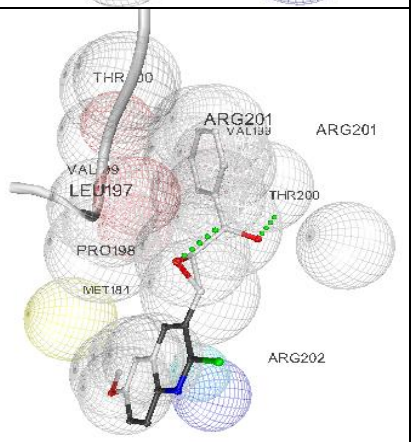
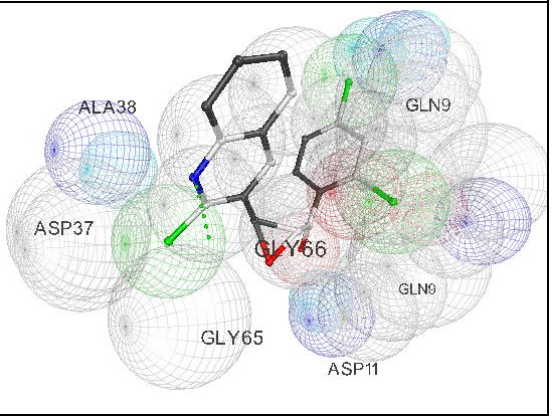
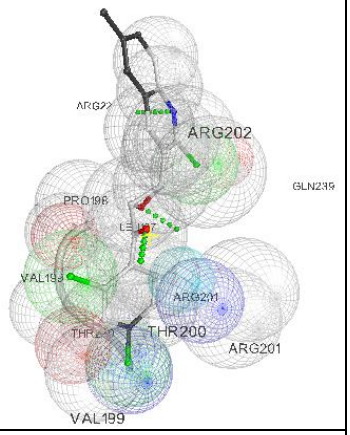
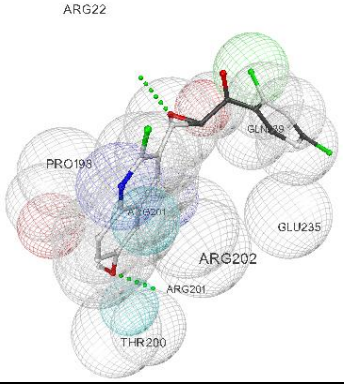
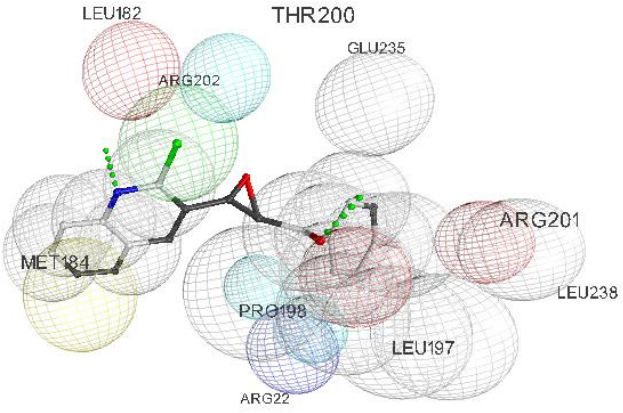
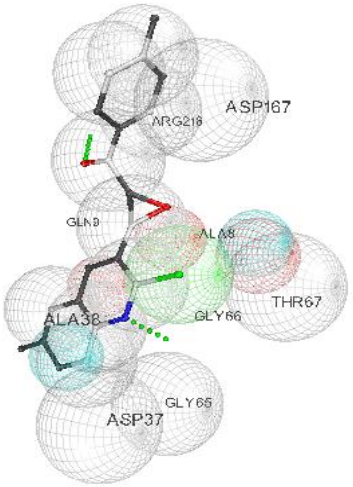
Fluconazole	

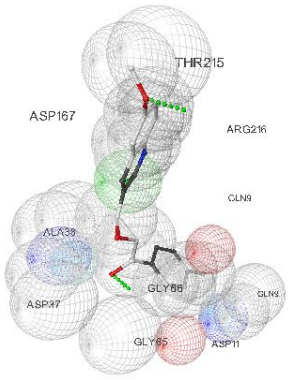
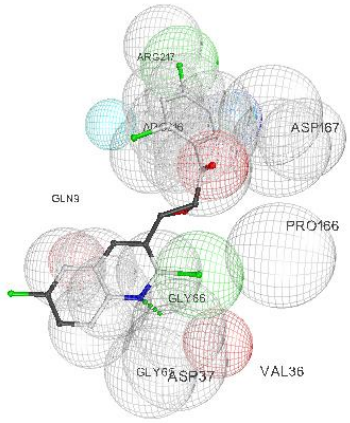
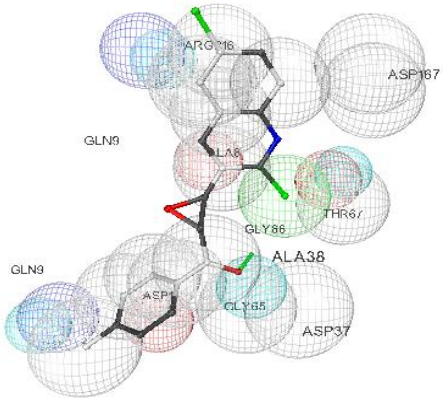
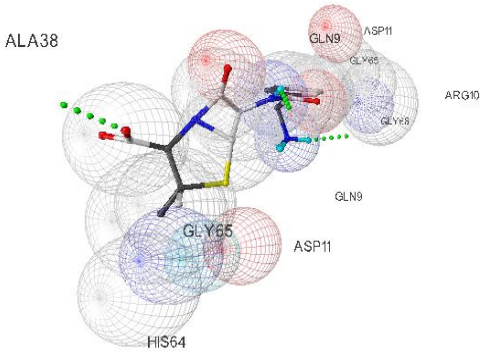
Figure 6. Interacting sites of *cis*-epoxides 1-11 with GlcN-6-P synthase

Table 11. Molecular docking of *trans*-1 to *trans*-11 with glucosamine-6-phosphate synthase

Molecule	Binding energy	Docking energy	Inhibitory constant	Intermol energy	H- bonds	Bonding
1	-8.61	-9.66	4.88e-007	-9.54	3	1a::DRG:OAN:GPS:B:GLU235:OE1 1a::DRG:OAP:GPS:B:THR200:HG1 1a::DRG:OAP:GPS:B:ARG201:HN
2	-9.44	-9.77	1.2e-007	-10.38	3	2a::DRG:OAN:GPS:A:ARG201:HH22 2a::DRG:OAP:GPS:B:THR200:HG1 2a::DRG:OAP:GPS:B:ARG201:HN
3	-8.65	-9.78	4.57e-007	-9.89	2	3a::DRG:OAN:GPS:A:ARG201:HH22 3a::DRG:OAP:GPS:B:ARG201:HN
4	-6.85	-8.04	9.52e-006	-7.78	2	1b::DRG:OAN:GPS:A:ASP11:OD1 1b::DRG:NAG:GPS:A:GLY66:HN
5	-9.52	-10.54	1.05e-007	-10.45	3	2b::DRG:OAP:GPS:A:THR200:HG1 2b::DRG:NAG:GPS:B:ARG22:HH21 2b::DRG:OAN:GPS:B:ARG201:SS22
6	-7.34	-8.63	4.16e-006	-8.59	2	3b::DRG:OAY:GPS:A:ARG201:HN 3b::DRG:OAN:GPS:B:ARG22:HH21
7	-7.69	-8.78	2.29e-006	-8.63	2	1c::DRG:OAP:GPS:A:ARG201:HH22 1c::DRG:NAG:GPS:B:ARG202:HH21
8	-8.22	-9.29	9.35e-007	-9.16	2	2c::DRG:NAG:GPS:A:GLY66:HN 2c::DRG:OAP:GPS:A:ARG216:HH12
9	-8.3	-9.54	8.21e-007	-9.55	3	3c::DRG:OAX:GPS:A:ASP167:O 3c::DRG:OAP:GPS:A:GLY66:HN 3c::DRG:OAX:GPS:A:ARG216:HN
10	-9.12	-10.33	2.08e-007	-10.05	2	5b::DRG:OAN:GPS:A:ALA8:O 5b::DRG:NAG:GPS:A:GLY66:HN
11	-7.81	-8.99	1.9e-006	-8.74	2	5c::DRG:OAN:GPS:A:GLN9:O 5c::DRG:OAP:GPS:A:GLY66:HN
Ampicillin	-6.14	-7.05	3.16e-005	-7.38	3	Ampicillin::DRG:H:GPS:A:GLN9:O Ampicillin::DRG:HBP:GPS:B:GLN9:O Ampicillin::DRG:OAX:GPS:A:ALA38:HN
Flucanazole	-8.14	-7.69	1.07e-006	-9.7	5	Fluconazole::DRG:NAS,OAP:GPS:A:ARG201:H22 Fluconazole::DRG:NAU:GPS:B:THR200:HG1 Fluconazole::DRG:NAK:GPS:B:ARG202:HE Fluconazole::DRG:NAK:GPS:B:ARG202:HH21 Fluconazole::DRG:NAU:GPS:B:ARG201:HN

1	 ARG201 ARG201 THR200 GLU235 VAL199 THR200 VAL199 PRO198 ARG22 MET184
2	 ARG201 VAL199 ARG201 THR200 VAL199 PRO198 ARG22 GLU18 ARG202
3	 THR200 ARG201 VAL199 ARG201 VAL199 LEU197 THR200 PRO198 MET181 ARG202
4	 ALA38 GLN9 ASP37 GLY66 GLN9 GLY65 ASP11

5	 ARG22 ARG202 GLN239 PRO196 LEU197 VAL199 ARG201 THR200 ARG201 VAL199
6	 ARG22 GLN239 PRO196 GLU235 ARG202 ARG201 THR200
7	 LEU182 THR200 GLU235 ARG202 ARG201 MET184 LEU238 PRO196 LEU197 ARG22
8	 ASP167 ARG218 GLN9 ALA8 THR67 ALA38 GLY66 GLY65 ASP37

9	
10	
11	
Ampicillin	

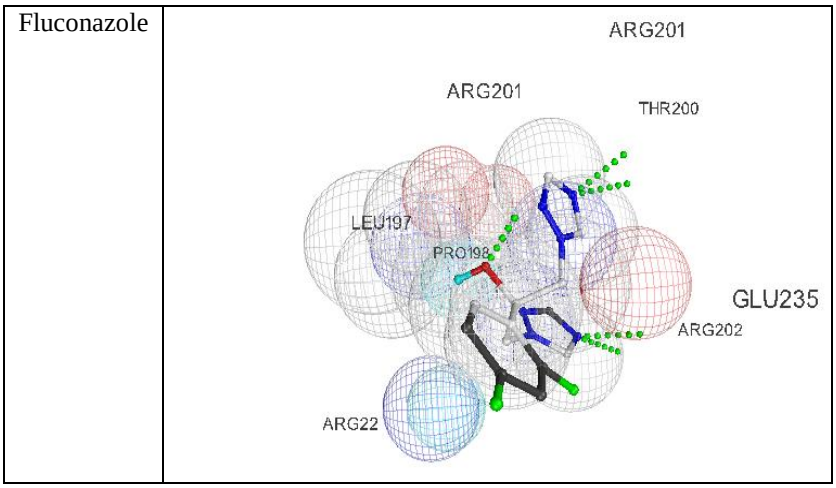


Figure 7. Interacting sites of *trans*-epoxides 1-11 with GlcN-6-P synthase

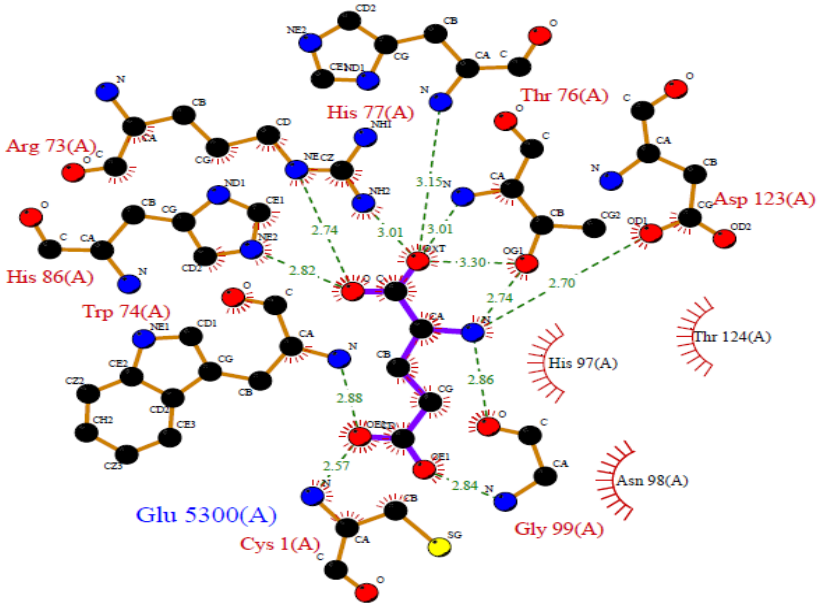


Figure 8. Interacting amino acids as predicted from the ligplot.

IV. CONCLUSION

The present study shows that it is easy to synthesize epoxides **1-11** with the quinoline/substituted quinoline moiety on one side and benzoyl/substituted benzoyl group on the other side by treating 2-chloroquinoline-3-carbaldehydes in DMF solvent with 1-aryl-2-bromoethanones in presence of K_2CO_3 as the basic catalyst and at room temperature. This is the mildest possible condition for Darzens reaction involving chloroquinolinecarbaldehydes and phenacyl bromides. The products (**1-11**), like many other quinoline containing compounds have been found by *in vitro* as well as *in silico* methods to possess a number of pharmacological properties. The *in vitro* work includes investigation of their ability to scavenge DPPH and ABTS free radicals, activity against pathogenic bacteria and fungi, toxicity against brine shrimp nauplii and ability to cleave super coiled DNA. These experimental results were corroborated by molecular modeling studies that included calculation of compliance of Lipinski's Rule of Five, oral rat LD_{50} values by different methods, bioactivity by Molinspiration programme and analysis of docking to the enzyme GlcN-6-P synthase. From the results of all these studies, we conclude that the quinolinyl epoxy ketones described here have good potential to be considered for further studies by *in vivo* methods. The antimicrobial activity and toxicity evaluation experiments strongly indicate that some of them are promising molecules for further investigation as antifungal and anticancer agents.

ACKNOWLEDGEMENTS

The authors are thankful to the authorities of Jain University for encouragement and financial support for this work, and Professor S.Chandrasekaran, Department of Organic Chemistry, Indian Institute of Science for providing HRMS data.

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