Synthesis, crystal structure, ABTS radical-scavenging activity, antimicrobial and docking studies of some novel quinoline derivatives

ARTICLE *in* JOURNAL OF MOLECULAR STRUCTURE · JULY 2014

Impact Factor: 1.6 · DOI: 10.1016/j.molstruc.2014.04.009

Journal of Molecular Structure 1070 (2014) 10–20

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Synthesis, crystal structure, ABTS radical-scavenging activity, antimicrobial and docking studies of some novel quinoline derivatives

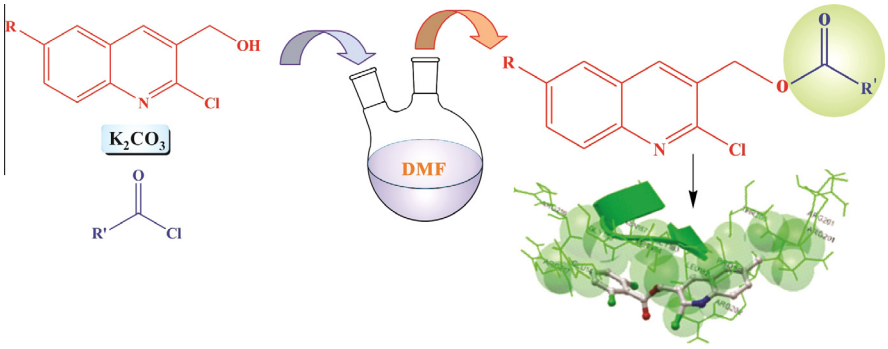
Sumaiya Tabassum [a], T.H. Suresha Kumara [a,b,*], Jerry P. Jasinski [c], Sean P. Millikan [c], H.S. Yathirajan [d], P.S. Sujan Ganapathy [e], H.B.V. Sowmya [a], Sunil S. More [f], Gopalpur Nagendrappa [a], Manpreet Kaur [d], Gilish Jose [a]

[a] P.G. Department of Chemistry, Jain University, 127/2, Bull Temple Road, Chamarajpet, Bangalore 560026, India
[b] Department of Chemistry, UBDT, College of Engineering, Davangere, Karnataka 577004, India
[c] Department of Chemistry, Keene State College, Keene, NH 03435-2001, USA
[d] Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570006, India
[e] Centre for Advanced Studies in Biosciences, Jain University, Bangalore 560019, India
[f] P.G. Department of Biochemistry, C.P.G.S., Jain University, Jayanagar 3rd block, Bangalore 560011, India

HIGHLIGHTS

- New series of 2-chloroquinolin-3-yl ester derivatives were synthesized.
- Chemical structures of the compounds were characterized by ^{1}H NMR, ^{13}C NMR, LCMS spectral analysis and elemental analysis.
- X-ray crystallographic study of **6a** and **6e** were carried out.
- *In vitro* antimicrobial and ABTS radical-scavenging activity screening were carried out.
- The docking studies were carried out.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 23 November 2013
Received in revised form 3 April 2014
Accepted 3 April 2014
Available online 18 April 2014

Keywords:
Vilsmeier–Haack reaction
Quinoline
Single crystal X-ray structure
Docking studies
Antimicrobial studies
ABTS Radical-scavenging activity

ABSTRACT

In this study, a series of nine novel 2-chloroquinolin-3-yl ester derivatives have been synthesized *via* a two-step protocol from 2-chloroquinoline-3-carbaldehyde. The structures of all these compounds were confirmed by spectral data. The single crystal X-ray structure of two derivatives, (2-chloroquinolin-3-yl)methyl acetate [**6a**] and (2-chloro-6-methylquinolin-3-yl)methyl acetate [**6e**] have also been determined. The synthesized compounds were further evaluated for their ABTS radical-scavenging activity and antimicrobial activities. Amongst all the tested compounds, **6a** exhibited maximum scavenging activity with ABTS. Concerning antibacterial and antifungal activities, compound (2-chloro-6-methoxyquinolin-3-yl)methyl 2,4-dichlorobenzoate [**6i**] was found to be the most active in the series against *B. subtilis*, *S. aureus*, *E. coli*, *K. pneumonia*, *C. albicans* and *A. niger* species. The structure-antimicrobial activity relationship of these derivatives were studied using Autodock.

Introduction

Quinoline is a remarkable, interesting nitrogen heterocyclic scaffold of paramount importance to human race. Its skeleton is

* Corresponding author. Tel.: +91 9916588466, mobile: +91 09916588466.
E-mail address: suresha.kumara@gmail.com (T.H. Suresha Kumara).

http://dx.doi.org/10.1016/j.molstruc.2014.04.009
0022-2860/

often an attractive framework in the design of several synthetic compounds against diverse pharmacological targets leading to the discovery of potent drugs. The chemistry of quinoline and its derivatives have been enjoying a relative renaissance of interest due to the growing abundance of quinoline components in various natural products, pharmaceuticals and new materials. The utility of quinoline derivatives in the areas of medicine [1], food, catalyst, dye [2], materials, refineries and electronics [3,4] is well established. These compounds are found to possess various bioactivities such as anti-malarial [5–7], anti-bacterial [8–11], anti-fungal [12–14], anti-cancer agents [15–18]. They are widely used as antibiotics [19], alkaloids, rubber, chemicals and flavoring agents. Additional industrial applications include their use as corrosion inhibitors, preservatives [20], solvents, resins, transition metal complex catalyst for uniform polymerization and luminescence chemicals [21]. The literature survey revealed that, the synthetic quinoline and substituted quinoline derivatives are associated with a wide range of biological properties in curing a lot of diseases. Amongst them, quinoline esters are one of the most important derivatives, however only few methods have been reported in the literature [22–32] for their synthesis. Recently, quinoline-4-methyl esters are found to serve as human nonpancreatic secretory phospholipase A2 inhibitors [33] and quinoline dicarboxylic esters are used as biocompatible fluorescent tags [34]. As a result, the synthesis of quinoline and its derivatives have always attracted considerable attention especially from biochemists and synthetic organic chemists who are concerned with human and animal health care problems. In view of these observations and with a view to further explore the pharmacological profile of this class of compounds, the present study aims to put in considerable efforts to synthesize 2-chloroquinolin-3-yl ester derivatives, purify and characterize them. As quinoline and substituted quinoline derivatives are known to exhibit various biological activities such as antimicrobial, anti-inflammatory, analgesic, anti-tuberculosis, antiviral, the proposed research work is expected to result in the synthesis of biologically active of these derivatives. We also herein report, the crystal structures of two derivatives, the crystal structure analysis was carried out with the intention of eliciting structural information which could facilitate further understanding of structural requirements for improved biological activity, ABTS radical-scavenging activity and antimicrobial activity of the synthesized derivatives.

Oxidative stress generates reactive oxygen species, such as superoxide (O_2^-), hydroxyl (OH^-) and peroxyl (OOH^-, ROO^-) radicals, and are a crucial etiological factor to the pathophysiology of a variety of degenerative or pathological conditions such as ageing, cancer, coronary heart disease, Alzheimer's disease, atherosclerosis and inflammation [35–36]. Human body has multiple mechanisms especially enzymatic and non-enzymatic antioxidant systems to protect the cellular molecules against reactive oxygen species (ROS) induced damage [37]. However due to the overproduction of reactive species and/or inadequate antioxidant defense, it culminates in severe or continued oxidative stress. The harmful action of the free radicals can, however be blocked by antioxidant substances, which scavenge the free radicals and detoxify the organism [38]. Many synthetic antioxidants such as butylated hydroxyl anisole (BHA) and butylated hydroxyl toluene (BHT) are very effective and have been added to food stuffs during food processing but they may possess toxic side effects and also acts as carcinogens [39]. Therefore there is a necessity to synthesize potent compounds that would have better scavenging activity and possess fewer side effects.

Infectious diseases are threatening millions of people around the world and the recent upsurge in widespread antibiotic resistance among pathogens [40–42] and the undesirable side effects associated with constant use of drugs has prompted the search for novel antimicrobial agents. In virtual screening, a molecular docking played a crucial role in finding putative binding protein for a compound either from genomic or protein database [43]. Auto Dock 3 was used to perform the docking of a set of molecules with-glucosamine-6-phosphate synthase(GlcN-6-P synthase), an elite target protein to inhibit the growth of microbes. This is the first report exploring the biological potential of these synthesized molecules as antimicrobial agents and providing evidence for exploitation of these compounds for further therapeutic applications.

Experimental

General procedures

Open capillary method was employed to determine the melting points and were found uncorrected. The NMR spectra was recorded at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR), referenced to an internal standard (TMS) or residual solvent protons and chemical shifts (δ) reported in ppm. Mass spectra were recorded on LC–MS (Shimadzu QP 5000 spectrometer). CHN analysis was performed using Elementar vario MICRO cube analyzer. All chromatographic purifications were performed on 60–120 silica gel columns by using 9.5:0.5 ratio of petroleum ether and ethyl acetate as eluent. Samples were recrystallized from DCM or ethyl acetate. Chemicals and solvents used for the chemical synthesis were acquired from commercial sources of analytical grade.

*Synthesis of 2-chloroquinoline-3-carbaldehyde (**4a**) [44–55]*

To a stirred solution of N-phenylacetamide(**3a**) (5 mmoles) in dry DMF (15 mmoles), $POCl_3$ (60 mmoles) was added drop-wise. The mixture was refluxed for overnight on water bath at 85–90 °C. The reaction mixture was quenched with crushed ice present in a 500 mL beaker and stirred well for some time. The precipitate obtained was filtered, dried and purified by recrystallization processby using ethyl acetate to afford pure compound **4a** in 82% yield. Similarly, the other aldehydes **4b–c** were prepared by using the procedures reported earlier.

*Synthesis of (2-chloroquinolin-3-yl)methanol (**5a**) [56–59]*

To a stirred mixture of2-chloroquinoline-3-carbaldehydes (**4a**) (0.052 mol) in methanol (6 mL), $NaBH_4$ (0.078 mol) was added portion wise under ice cold conditions for 15 min. The reaction mixture was stirred for 30 min. After the completion of reaction, the reaction mixture was quenched with ice cold water and acidified very slowly with dil. HCl. The solid obtained was filtered, washed, dried and recrystallized from dichloromethane to afford pure compound **5a** in 80% yield. Similarly, the other alcohols **5b–c** were prepared by using the procedures reported earlier.

*Synthesis of (2-chloroquinolin-3-yl)methyl acetate (**6a**)*

A mixture of (2-chloroquinolin-3-yl)methanol (**5a**) (0.20 g, 0.00095 mol) and acid chloride (0.21 g, 0.0028 mol) was stirred in DMF along with activated K_2CO_3 at room temperature. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with ice cold water. The obtained solid was filtered, washed, dried and further purified by column chromatography using 9.5:0.5 mixture of petroleum ether and ethyl acetate to afford pure product **6a** in 56% yield. Similarly, the other esters **6b–I** were prepared (Table 1).

*Spectral dataof(2-chloroquinolin-3-yl)methyl acetate derivatives (**6a–i**)*

*(2-Chloroquinolin-3-yl)methyl acetate (**6a**)*

White crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 0.4 Hz, 1H), 8.04–8.02 (m, 1H), 7.84 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.75–7.73 (m, 1H), 7.57–7.56 (m, 1H), 5.35 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 150.1, 147.7, 138.5, 131.2, 128.8, 128.2, 128.0, 127.8, 127.4, 63.5, 21.3; MS (*m/z*): 236.1 $[M+2H]^+$; Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16, H, 4.28, N, 5.94; found: C, 61.05, H, 4.13, N, 5.79.

*(2-Chloroquinolin-3-yl)methyl benzoate (**6b**)*

Off white powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, *J* = 8.2 Hz, 1H), 8.13 (t, *J* = 8.0 Hz, 1H), 8.06–8.03 (m, 2H), 7.96–7.94 (m, 1H), 7.87 (t, *J* = 9.6 Hz, 1H), 7.79 (s, 2H), 7.50–7.48 (m, 2H), 5.65 (d, *J* = 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 149.8, 147.4, 138.2, 133.4, 130.8, 129.8, 129.7, 128.8, 128.6, 128.4, 128.3, 128.0, 127.7, 127.4, 127.0, 63.5; MS (*m/z*): 298.0 $[M+H]^+$; Anal. Calcd for $C_{17}H_{12}ClNO_2$: C, 68.58, H, 4.06, N, 4.70; found: C, 68.39, H, 4.19, N, 4.91.

*(2-Chloroquinolin-3-yl)methyl 2,4-dichlorobenzoate (**6c**)*

White crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.90-7.88 (m, 3H), 7.58 (t, *J* = 2.0 Hz, 1H), 7.51 (t, *J* = 2.4 Hz, 1H), 7.34–7.31 (m, 2H), 5.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 146.0, 139.5, 138.3, 137.7, 136.0, 133.5, 133.3, 132.9, 131.5, 131.2, 128.0, 127.2, 127.1, 126.7, 126.6, 64.4; MS (*m/z*): 364.0 $[M+H]^+$; Anal. Calcd for $C_{17}H_{10}Cl_3NO_2$: C, 55.69, H, 2.75, N, 3.82; found: C, 55.47, H, 2.84, N, 3.92.

*(2-Chloroquinolin-3-yl)methyl 2,6-dichlorobenzoate (**6d**)*

White powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.74–7.73 (m, 1H), 7.57–7.56 (m, 1H), 7.29–7.27 (m, 3H), 5.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 149.5, 147.4, 138.5, 133.0, 132.1, 131.3, 131.0, 128.4, 128.1, 128.0, 127.7, 127.4, 127.0, 126.8, 126.6, 64.6; MS (*m/z*): 365.8 $[M+H]^+$; Anal. Calcd for $C_{17}H_{10}Cl_3NO_2$: C, 55.69, H, 2.75, N, 3.82; found: C, 55.49, H, 2.86, N, 3.90.

*(2-Chloro-6-methylquinolin-3-yl)methyl acetate (**6e**)*

White crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 4.8 Hz, 2H), 5.33 (s, 2H), 2.54 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 148.7, 145.9, 137.5, 137.4, 133.0, 128.0, 127.7, 127.1, 126.5, 63.1, 27.2, 20.7; MS (*m/z*): 250.0 $[M+H]^+$; Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53, H, 4.84, N, 5.61; found: C, 62.17, H, 4.79, N, 5.66.

*(2-Chloro-6-methylquinolin-3-yl)methyl benzoate (**6f**)*

Yellow crystal; ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.16–8.13 (m, 1H), 7.96 (d, *J* = 11.6 Hz, 2H), 7.60–7.59 (m, 1H), 7.50 (t, *J* = 9.6 Hz, 3H), 7.28 (d, *J* = 2.0 Hz, 2H), 5.61 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.2, 151.1, 146.0, 137.6, 137.5, 133.4, 133.1, 131.1, 130.3, 129.9, 129.8, 128.6, 128.0, 127.8, 127.1, 126.6, 63.6, 24.0; MS (*m/z*): 312.0 $[M+H]^+$; Anal. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53, N, 4.49; found: C, 69.47; H, 4.50, N, 4.41.

*(2-Chloro-6-methylquinolin-3-yl)methyl 2,6-dichlorobenzoate (**6g**)*

White crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 1.6 Hz, 2H), 7.29–7.27 (m, 3H), 5.63 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 148.6, 146.0, 143.0, 137.9, 137.5, 135.2, 133.2, 133.1, 132.1, 131.2, 128.0, 127.0, 126.8, 126.6, 126.1, 64.6, 21.6; MS (*m/z*): 382.0 $[M+H]^+$; Anal. Calcd for $C_{18}H_{12}Cl_3NO_2$: C, 56.80; H, 3.18, N, 3.68; found: C, 56.89; H, 3.26, N, 3.53.

*(2-Chloro-6-methoxyquinolin-3-yl)methyl acetate (**6h**)*

White powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.09 (s, 1H), 5.33 (s, 2H), 3.93 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 158.4, 147.0, 143.3, 136.8, 129.7, 128.2, 128.0, 123.4, 105.2, 63.1, 55.7, 20.9; MS (*m/z*): 266.0 $[M+H]^+$; Anal. Calcd for $C_{13}H_{12}ClNO_3$: C, 58.77; H, 4.55, N, 5.27; found: C, 58.86; H, 4.58, N, 5.14.

*(2-Chloro-6-methoxyquinolin-3-yl)methyl 2,4-dichlorobenzoate (**6i**)*

Pale brown powder; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.91–7.89 (m, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.33 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.09 (d, *J* = 2.8 Hz, 2H), 5.58 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 157.5, 146.1, 142.5, 137.9, 136.5, 134.2, 131.8, 130.2, 128.7, 127.1, 126.7, 126.4, 126.2, 122.6, 104.2, 63.4, 54.6; MS (*m/z*): 396.0 $[M+H]^+$; Anal. Calcd for $C_{18}H_{12}Cl_3NO_3$: C, 54.50; H, 3.05, N, 3.53; found: C, 54.43; H, 3.09, N, 3.59.

X-ray crystallography

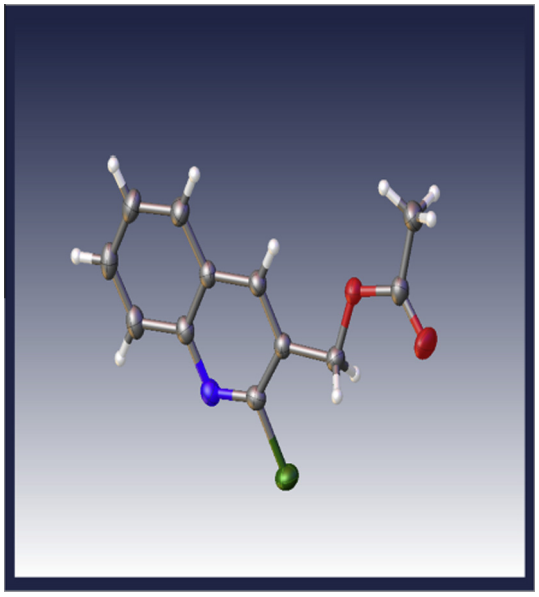
Single crystal of **$C_{12}H_{10}ClNO_2$ [6a]** was obtained by slow evaporation of its ethyl acetate solution at 303 K and single crystal of **$C_{13}H_{12}ClNO_2$ [6e]**, by the slow evaporation of its dichloromethane solution at 283 K. A suitable crystal was selected and placed on a Nylon Loop on an Xcalibur, Eos, Gemini X-ray diffractometer. The crystal was kept at 173(2) K during data collection. Using Olex2 [60], the structure was solved with the Superflip [61] structure solution program using Charge Flipping and refined with the ShelXL [62] refinement package using Least Squares minimization. The details are presented in Tables 2a and 2b.

Table 1
Synthesis of 2-chloroquinolin-3-yl ester derivatives (**6a–i**).

Compounds	*R*	R^1	Reaction time for completion	m.p. (°C)	Yield (%)
6a	—H	—CH_3	2 h	75	56
6b	—H	—C_6H_5	1 h	136	70
6c	—H	-2,4 Dichlorobenzoyl	1 h	134	73
6d	—H	-2,6 Dichlorobenzoyl	2 h	146	70
6e	—CH_3	—CH_3	o	85–87	50
6f	—CH_3	—C_6H_5	o	126	74
6g	—CH_3	-2,6 Dichlorobenzoyl	o	175	74
6h	—OCH_3	—CH_3	o	112	76
6i	—OCH_3	-2,4 Dichlorobenzoyl	o	148	73

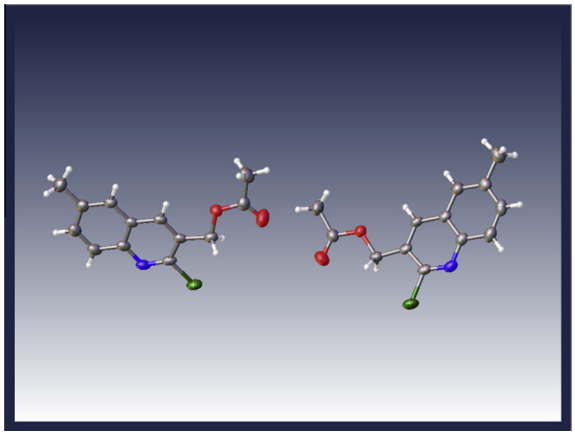
o = Overnight.

*Crystal structure determination of [**6a**]*



Crystal Data for $C_{12}H_{10}NO_2Cl$ (M = 235.66): Monoclinic, space group $P2_1/c$ (No. 14), a = 8.1324(4) Å, b = 10.9545(4) Å, c = 12.1817(5) Å, β = 93.323(4)°, V = 1083.40(8) Å^3, Z = 4, T = 173(2) K, μ(Mo Kα) = 0.335 mm^{-1}, D_{calc} = 1.445 g/mm^3, 13,335 reflections measured ($6.7 \leqslant 2\theta \leqslant 65.78$), 3727 unique ($R_{int}$ = 0.0303) which were used in all calculations. The final R_1 was 0.0421 ($I > 2\sigma(I)$) and wR_2 was 0.1160 (all data).

*Crystal structure determination of [**6e**]*



Crystal Data for $C_{13}H_{12}ClNO_2$ (M = 249.69): Monoclinic, space group $P2_1/c$ (No. 14), a = 24.0571(7) Å, b = 7.5420(2) Å, c = 13.6211(4) Å, β = 103.070(3)°, V = 2407.37(12) Å^3, Z = 8, T = 173(2) K, μ(Cu Kα) = 2.724 mm^{-1}, D_{calc} = 1.378 g/mm^3, 13,833 reflections measured ($11.328 \leqslant 2\theta \leqslant 144.99$), 4705 unique ($R_{int}$ = 0.0359) which were used in all calculations. The final R_1 was 0.0587 ($I > 2\sigma(I)$) and wR_2 was 0.1642 (all data).

ABTS assay [63]

ABTS [2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)] Radical Cation Scavenging Method.

Principle:

The pre-formed radical mono cation of 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) is generated by oxidation of ABTS with potassium persulfate (a blue chromogen) and is reduced in the presence of such hydrogen donating antioxidants.

Chemicals and Reagents Used:

Preparation of ABTS solution

Solution I: ABTS (2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (2 mM solution is prepared using distilled water).

Solution II: Potassium persulfate (17 mM solution is prepared using distilled water).

0.3 mL of solution II was added to 50 mL of solution I. The reaction mixture was left to stand at room temperature overnight in dark before use.

Preparation of Test Solution

5 mg of each of the drug samples and the standard (ascorbic acid) were accurately weighed separately and dissolved in 1 mL of Dimethyl sulphoxide (DMSO).

Method

1 mL of distilled DMSO was added to 0.2 mL of various concentrations of the drug samples or standard, and 0.16 mL of ABTS solution was added to make a final volume of 1.36 mL. The absorbance was measured spectrophotometrically, after 7 min at 734 nm using a Spectrophotometer. Blank was maintained without ABTS.

The radical scavenging activity (%) is calculated by the following formula,

$$\frac{(\text{Absorbance of control} - \text{Absorbance of sample})}{\text{Absorbance of control}} \times 100$$

Bacterial susceptibility testing

In vitro antibacterial activity of synthesized compounds was studied against Gram-negative and Gram-positive bacteria by the agar well diffusion [64]. Nutrient agar (Hi Media, India) was used as the bacteriological medium. The compounds were dissolved in 10% aqueous dimethylsulfoxide (DMSO) to a final concentration of 100 μg/100 μL. Pure DMSO was taken as the negative control and 100 μg/100 μL Streptomycin as the positive control.

100 μL of inoculum 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. 100 μL of test and control compound 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 [65,66]. The diameter of the zone of inhibition produced by each agent were measured with a ruler and compared with those produced by the commercial antibiotic Streptomycin.

Fungal susceptibility testing

The antifungal activity of the synthesized compounds was tested using agar well diffusion method. The potato dextrose agar plates were inoculated with each fungal culture (10 days old) by point inoculation. A well of about 6.0 mm diameter with sterile cock borer was aseptically punched on each agar plate. The synthesized test compound (100 μg/100 μL) was introduced into the well; a negative control well was too made with 100 μL of the solvent DMSO and 100 μg/100 μL Nystatin as the positive control. Plates were kept in laminar flow for 30 min for pre diffusion of compound to occur and then incubated at 28 °C for 48 h. Resulting zone of inhibition (in mm) was measured using a Hi media zone scale [67].

Molecular docking studies

Automated docking was used to determine the orientation of inhibitors bound in the active site of GlcN-6-P synthase as target for antimicrobial activity. A Lamarckian genetic algorithm method, implemented in the program AutoDock 3.0, was employed. The

ligand molecules (**6a–i**) were designed and the structure was analyzed by using ChemDraw Ultra 6.0. 3D coordinates were prepared using PRODRG server [68]. The protein structure file (PDB ID: 1XFF) was taken from PDB (www.rcsb.org/pdb) was edited by removing the hetero-atoms, adding C terminal oxygen [69]. For docking calculations, Gasteigere – Marsili partial charges [70] were assigned to the ligands and non-polar hydrogen atoms were merged. All torsions were allowed to rotate during docking. The grid map was centered at particular residues of the proteins which was predicted from the ligplot and were generated with AutoGrid. The Lamarckian genetic algorithm and the pseudo-Solis and Wets methods were applied for minimization, using default parameters [71].

Results and discussion

For synthesis

Synthesis of the derivatives **(6a–i)** was carried out as depicted in Scheme 1. Quinoline carbaldehydes (**4a–c**) were synthesized through traditional Vilsmeier–Haack cyclization [35–46] of acetanilides (**3a–c**) [72]. These compounds were then reduced using $NaBH_4$ in methanol to yield (2-chloroquinolin-3-yl)methanol derivatives (**5a–c**). The analytical data of the compounds **4a–c** and **5a–c** was compared with the reports available in the literature [44–59]. The strategy employed for the synthesis of compounds (**6a–i**) is almost similar to that reported earlier [73]. Various quinoline ester derivatives (**6a–i**) were prepared by coupling alcohols (**5a–c**) with various acid chlorides in the presence of K_2CO_3 in DMF (Table 1). The IR spectra of compounds **(6a–i)** showed a peak around at 1750 cm^{-1} due to C=O stretching. The ^1H NMR spectra of compound **6a** showed a shift at $\delta = 3.92$ (s, 3H) for the protons CH_3CO. The LC–MS m/z value of $[M]^{2+}$ was obtained at 236.1. Finally the ^{13}C NMR spectra of the compound **6a** showed a signal at nearly $\delta = 170$ ppm for the carbonyl group. The detailed procedure and the analytical data for all the derivatives **(6a–i)** are placed in experimental section. The crystal structures of the compounds **6a** and **6e** were also determined. Further, supporting data for all the final derivatives **6a–i**, i.e. scanned copies of ^1H NMR, ^{13}C NMR and LC–MS spectra are enclosed.

X-ray crystal structure analysis

*(2-Chloroquinolin-3-yl)methyl acetate (**6a**)*

In **$C_{12}H_{10}NO_2Cl$**, the dihedral angle between the mean planes of the 2-chloroquinolin-3-yl and the carboxylate group (C10\O1\C11\O2) is 12.8(5)° (Fig. 1).

Bond lengths are in normal ranges [74] (Table 2a). In the crystal, weak C7—H7···N1 intermolecular interactions (Table 3) link the molecules into tetramers and influence the crystal packing (Fig. 2).

Symmetry transformations used to generate equivalent atoms: (i) $1-x, -1/2+y, 1/2-z$; (ii) $1-x, -y, 1-z$.

*(2-Chloro-6-methylquinolin-3-yl)methyl acetate (**6e**)*

In **$C_{13}H_{12}ClNO_2$**, two independent molecules [A and B] crystallize in the asymmetric unit. The dihedral angle between the mean planes of the 2-chloro-6-methylquinolin-3-yl and the carboxylate group is 10.9(3)°[A] and 7.0(9)° [B] (Fig. 3).

Bond lengths are in normal ranges [74] (Table 2b). The chlorine atoms in [A] and [B] are slightly deviated from the mean planes of the 2-chloro-6-methylquinolin-3-ylrings by 2.9(9)° and 2.8(8)°, respectively. In the crystal, weak C7B—H7B···O1A intermolecular interactions (Table 3) link the molecules into dimers along [1 0 0] (Fig. 4).

In addition Cg1—Cg1π—π intermolecular interactions are observed and contribute to crystal packing (Cg1—Cg1 = 3.8029(13) Å; $2-x, -y, 1-z$; Cg1 = N1A/C4A/C3A/C11A/C10A/C5A).

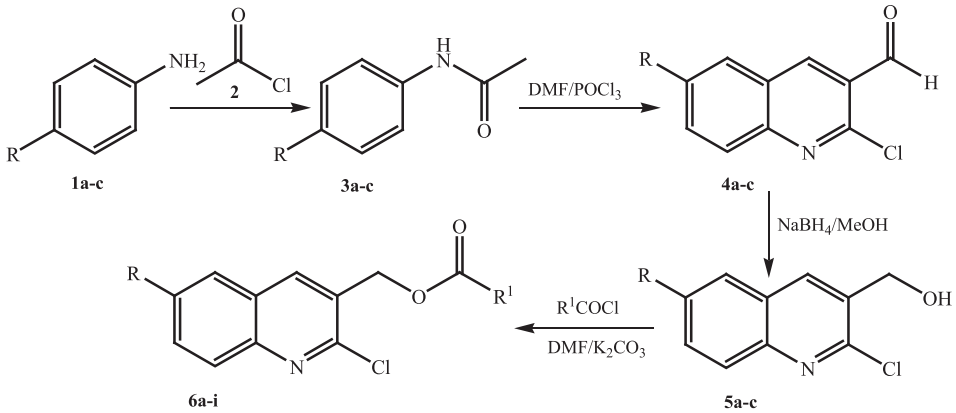
For ABTS radical-scavenging activity and antimicrobial activity

The ABTS radical-scavenging activityof the compounds (**6a–i**) revealed that amongst all the tested compounds, **6a** and **6g** exhibited maximum scavenging activity with ABTS. Compounds **6d–f** and **6h**, exhibited similar activity (Table 4).

Antimicrobial studies

The synthesized compounds were effective in controlling the growth of clinical strains tested (Table 5). The study revealed that the antibacterial activity of compound **6i** was highest with zone of inhibition in the range of 32.24 ± 0.18 to 18.67 ± 0.69. The lowest inhibition values were recorded by compound **6g** (13.87 ± 0.28 to 5.53 ± 0.24). The rest of the compounds i.e., **6a–f** and **6h** showed moderate activity. *Staphylococcus aureus* was the most susceptible and *Klebsiellapneumoniae*, the least amongst all the bacterial strains investigated in the present work. Streptomycin which was used as positive experimental control against strains assayed, produced a zone of inhibition of 45.33 ± 0.63 to 28.53 ± 0.17, while no inhibitory effect could be observed for DMSO used as negative control.

All the compounds exhibited different antifungal activity *in vitro* against the tested fungal strains (Table 5). Of these fungal strains, *Candida albicans* was more resistant to the synthesized compounds than *Aspergillus niger*. All the compounds produced the inhibitory zones; the most active compound being **6i** with



Scheme 1. Preparation of 2-chloroquinolin-3-yl ester derivatives (**6a–i**).

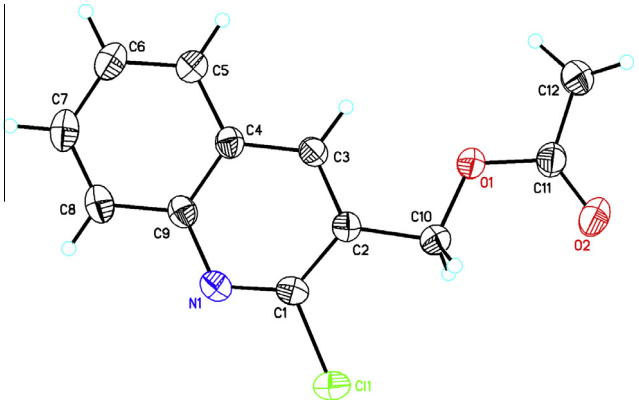


Fig. 1. Molecular structure of $C_{12}H_{10}NO_2Cl$ showing the atom labeling scheme and 50% probability displacement ellipsoids.

Table 2a
Selected crystal bond lengths (Å), bond angles (°), and torsion angles (°) for $C_{12}H_{10}NO_2Cl$.

C(l1)—C(1)	1.7468(13)
C(1)—C(2)	1.4181(16)
O(1)—C(10)	1.4356(15)
C(2)—C(10)	1.5018(17)
O(2)—C(11)	1.1953(18)
C(5)—C(6)	1.3702(19)
N(1)—C(1)	1.2987(16)
C(11)—C(12)	1.492(2)
C(11)—O(1)—C(10)	117.29(10)
C(1)—N(1)—C(9)	117.13(11)
N(1)—C(1)—Cl(1)	115.66(9)
N(1)—C(1)—C(2)	126.70(12)
C(2)—C(1)—Cl(1)	117.63(9)
C(3)—C(2)—C(1)	116.05(11)
N(1)—C(9)—C(4)	121.62(11)
N(1)—C(9)—C(8)	119.11(12)
O(1)—C(11)—C(12)	110.51(12)
O(2)—C(11)—O(1)	123.07(13)
O(2)—C(11)—C(12)	126.41(13)
O(1)—C(10)—C(2)	106.56(10)
Cl(1)—C(1)—C(2)—C(3)	178.47(9)
Cl(1)—C(1)—C(2)—C(10)	−1.86(15)
N(1)—C(1)—C(2)—C(3)	−0.17(18)
N(1)—C(1)—C(2)—C(10)	179.50(11)
C(1)—N(1)—C(9)—C(4)	0.58(17)
C(1)—N(1)—C(9)—C(8)	−179.53(11)
C(10)—O(1)—C(11)—O(2)	−0.8(2)
C(10)—O(1)—C(11)—C(12)	178.40(11)
C(10)—C(2)—C(3)—C(4)	−178.66(11)
C(11)—O(1)—C(10)—C(2)	177.23(10)

maximum zone of inhibition in the range of 20.53 ± 0.66 to 16.67 ± 0.84 followed by the compounds **6f**, **6b**, **6h**, **6d**, **6a**, **6c**, **6e**; and **6g** exhibited minimum antifungal activity (6.67 ± 0.16 to 4.87 ± 0.22), when compared with Nystatin (29.53 ± 0.33 to 24.73 ± 0.57).

Hence, it is apparent that they have been found to be effective antimicrobial substances against a wide range of microorganisms. Their activity is probably due to their ability to react with extracellular and soluble proteins and to complex with bacterial cell walls [75]. From the results it can be concluded that **6i** is more effective than **6g** and proved to be a better antimicrobial agent of the nine compounds and can be used as a leading molecule in drug design i.e., in inhibiting these medically important microbial strains. Such screening of various compounds and identifying the active agents

Table 2b
Selected crystal bond lengths (Å), bond angles (°), and torsion angles (°) for $C_{13}H_{12}ClNO_2$.

Cl(1A)—C(4A)	1.754(3)
O(1A)—C(1A)	1.195(4)
O(2A)—C(1A)	1.337(3)
N(1A)—C(4A)	1.289(3)
C(1A)—C(13A)	1.491(4)
C(8A)—C(9A)	1.364(4)
Cl(1B)—C(4B)	1.750(3)
O(1B)—C(1B)	1.196(3)
O(2B)—C(2B)	1.442(3)
N(1B)—C(5B)	1.375(4)
C(1B)—C(13B)	1.498(4)
C(1A)—O(2A)—C(2A)	115.7(2)
C(4A)—N(1A)—C(5A)	117.1(2)
O(1A)—C(1A)—O(2A)	122.9(3)
O(2A)—C(1A)—C(13A)	111.4(3)
C(11A)—C(3A)—C(2A)	124.1(2)
C(11A)—C(3A)—C(4A)	115.2(2)
N(1A)—C(4A)—Cl(1A)	115.83(19)
N(1A)—C(4A)—C(3A)	127.2(2)
C(1B)—O(2B)—C(2B)	114.7(2)
C(4B)—N(1B)—C(5B)	117.0(2)
O(1B)—C(1B)—O(2B)	123.5(3)
O(2B)—C(1B)—C(13B)	111.3(2)
C(11B)—C(3B)—C(2B)	124.9(2)
C(11B)—C(3B)—C(4B)	115.3(2)
N(1B)—C(4B)—Cl(1B)	115.97(19)
N(1B)—C(4B)—C(3B)	127.1(2)
O(2A)—C(2A)—C(3A)—C(4A)	171.9(2)
O(2B)—C(2B)—C(3B)—C(4B)	172.6(2)
N(1A)—C(5A)—C(6A)—C(7A)	−177.6(2)
N(1B)—C(5B)—C(6B)—C(7B)	−177.3(2)
N(1A)—C(5A)—C(10A)—C(11A)	−1.6(3)
N(1B)—C(5B)—C(10B)—C(11B)	−1.3(4)
C(1A)—O(2A)—C(2A)—C(3A)	−167.1(2)
C(1B)—O(2B)—C(2B)—C(3B)	−173.6(2)

Table 3
Non-bonded interactions and possible hydrogen bonds in $C_{12}H_{10}NO_2Cl$ and $C_{13}H_{12}ClNO_2$ (Å, °). *(D-donor; A-acceptor; H-hydrogen).*

D—H···A	D—H	H···A	D···A	D—H···A
C7—H7···N1^{i}	0.93	2.59	3.5030(17)	167.1
C7B—H7B···O1A^{ii}	0.930(4)	2.55	3.391(4)	150.5

Symmetry transformations used to generate equivalent atoms: i) 1−x, −1/2+y, 1/2−z; ii) 1−x, −y, 1−z (*D-donor; A-Acceptor; H-hydrogen*).

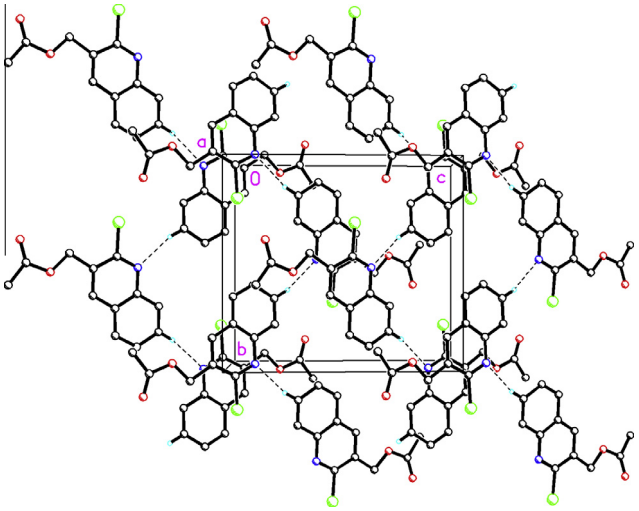


Fig. 2. Packing diagram of $C_{12}H_{10}NO_2Cl$viewed along *a*-axis. Dashed lines indicate weak C7—H7···N1 intermolecular interactions link the molecules into tetramers and influence the crystal packing. The remaining H atoms have been deleted for clarity.

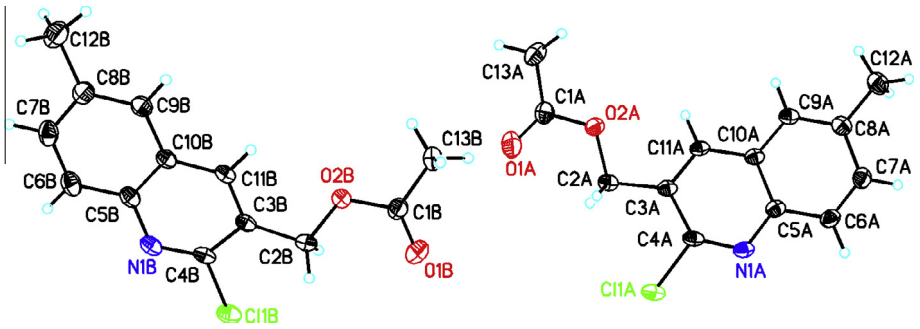


Fig. 3. Molecular structure of $C_{13}H_{12}ClNO_2$ showing the atom labeling scheme with two molecules (A and b) in the asymmetric unit and 30% probability displacement ellipsoids.

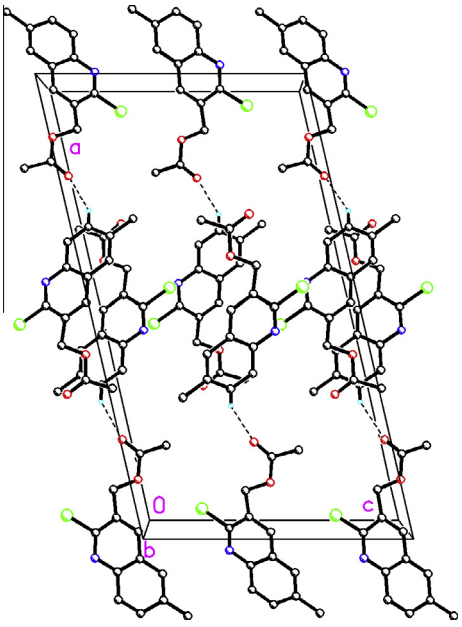


Fig. 4. Packing diagram of "$C_{13}H_{12}ClNO_2$" viewed along the *b* axis. Dashed lines indicate weak C7B—H7B···O1A intermolecular interactions link the molecules into dimers along [100]. The remaining H atoms have been deleted for clarity.

is essential because the successful prediction of a lead molecule and drug-like properties at the onset of drug design will pay off later in drug development.

Table 4
ABTS radical-scavenging assay of (**6a–i**) derivatives.

Sl no.	Compound	Scavenging activity (%)
1	**6a**	99.88
2	**6b**	96.33
3	**6c**	80.7
4	**6d**	99.08
6	**6e**	99.08
8	**6f**	99.08
9	**6g**	99.88
10	**6h**	99.08
11	**6i**	81.65

Docking studies

The docking of **6a–i** derivatives with Glutamine amido transferase domain reveals that, our synthesized molecule which are having inhibitory capability are exhibiting the interactions with one or the other amino acids in the active pockets which is showed in Fig. 5.

The docking results for inhibitor compounds are documented in Table 6.

Practically, all the nine molecules showed good binding energy and docking energy ranging from −7.84 kJ mol^{-1} to −10.36 kJ mol^{-1} and −8.81 kJ mol^{-1} to −11.01 kJ mol^{-1} respectively. Amongst the nine molecules, docking of GlcN-6-P synthase with **6i** revealed five hydrogen bonds and its binding energy and docking energy were −9.71 kJ mol^{-1} and −10.98 kJ mol^{-1} respectively and it may be considered as good inhibitor of GlcN-6-P synthase. All the synthesized molecules were completely enfolded in the entire active pocket of

Table 5
Antimicrobial activity of synthesized compounds against microbial strains.

Compound	Bacterial strains				Fungal strains	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Klebsiella pneumoniae*	*Candida albicans*	*Aspergillus niger*
Streptomycin	32.66 ± 0.33	45.33 ± 0.63	30.68 ± 0.22	28.53 ± 0.17	–	–
Nystatin	–	–	–	–	24.73 ± 0.57	29.53 ± 0.33
6a	16.00 ± 0.56	20.20 ± 0.14	14.00 ± 0.15	11.67 ± 0.33	10.67 ± 0.59	14.00 ± 1.19
6b	18.73 ± 0.19	23.27 ± 0.55	15.67 ± 0.33	13.73 ± 0.10	12.00 ± 0.04	16.00 ± 0.27
6c	13.53 ± 0.28	18.20 ± 0.14	11.33 ± 0.32	10.67 ± 0.34	8.33 ± 0.16	11.07 ± 0.50
6d	17.33 ± 0.29	21.87 ± 0.28	14.67 ± 0.58	12.00 ± 0.66	11.00 ± 0.92	14.67 ± 0.58
6e	12.67 ± 0.53	17.67 ± 0.69	10.33 ± 0.32	9.87 ± 0.18	7.67 ± 0.25	10.00 ± 0.92
6f	19.53 ± 0.01	24.53 ± 0.17	16.00 ± 0.56	14.67 ± 0.51	12.77 ± 0.30	16.67 ± 0.63
6g	10.60 ± 0.23	13.87 ± 0.28	7.67 ± 0.25	5.53 ± 0.24	4.87 ± 0.22	6.67 ± 0.16
6h	18.00 ± 0.63	22.73 ± 0.20	15.00 ± 0.36	12.33 ± 0.19	11.47 ± 0.16	15.33 ± 0.40
6i	24.27 ± 0.30	32.24 ± 0.18	20.87 ± 0.30	18.67 ± 0.69	16.67 ± 0.84	20.53 ± 0.66

The values are the mean of three experiments ± S.E.

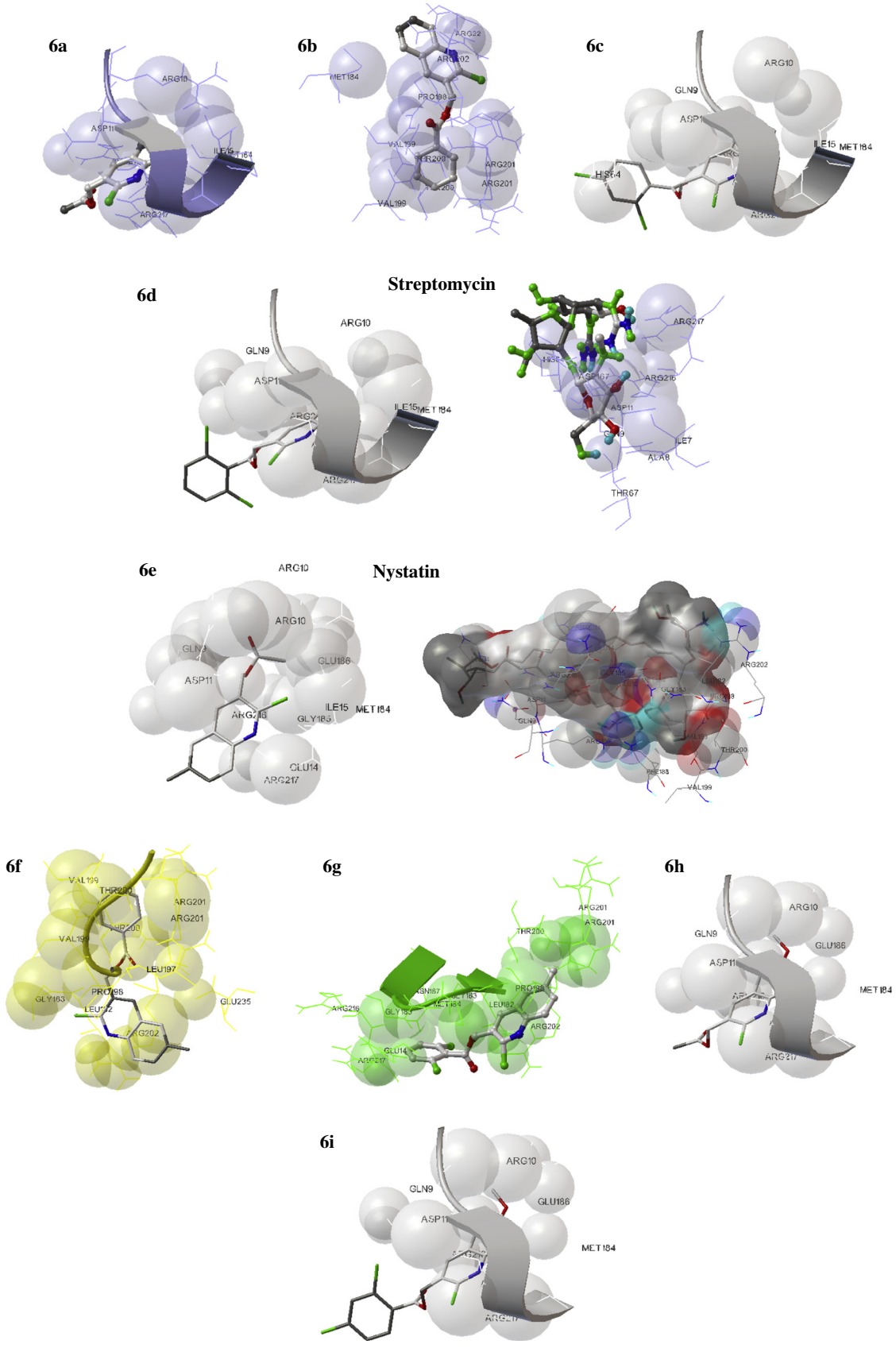


Fig. 5. Enfolding of synthesized molecules in the active pocket.

GlcN-6-P synthase (Fig. 5). The topology of the active site of GlcN-6-P synthase was similar in all the synthesized molecules, which is lined by interacting amino acids as predicted from the ligplot (Fig. 6).

In vitro studies reveals that **6i** has emerged as an active molecule against all the screened microorganisms, so it can be predicted that the activity may be due to the inhibition of enzyme GlcN-6-P

Table 6
Molecular docking results with glucosamine-6-phosphate synthase.

Molecule	Binding energy	Docking energy	Inhibitory constant	Internal energy	H-bonds	Bonding
6a	−7.98	−8.87	1.41e−006	−8.91	4	6a::DRG1:OAO:GPS:B:ARG217:HH22 6a::DRG1:NAG:GPS:A:GLU14:HN 6a::DRG1:OAO:GPS:B:ARG216:HH12 6a::DRG1:OAO:GPS:B:ARG216:HH22
6b	−10.0	−10.85	4.72e−008	−11.24	4	6b::DRG1:OAL:GPS:B:LEU195:O 6b::DRG1:OAO:GPS:A:THR200:HG1 6b::DRG1:OAL:GPS:B:ARG201:HH22 6b::DRG1:OAO:GPS:A:ARG201:HN
6c	−8.78	−10.13	3.65–007	−10.03	3	6c::DRG1:OAO:GPS:B:ARG217:HH22 6c::DRG1:OAO:GPS:B:ARG216:HH22 6c::DRG1:OAO:GPS:B:ARG216:HH12
6d	−8.53	−9.94	5.59e−007	−9.78	4	6d::DRG1:NAG:GPS:A:GLU14:HN 6d::DRG1:OAO:GPS:B:ARG217:HH22 6d::DRG1:OAO:GPS:B:ARG216:HH12 6d::DRG1:OAO:GPS:B:ARG216:HH22
6e	−7.84	−8.81	1.8e−006	−8.77	3	6e::DRG1:OAP:GPS:B:GLN9:HN 6e::DRG1:OAP:GPS:B:ARG10:HN 6e::DRG1:NAH:GPS:A:GLU14:OE1
6f	−10.36	−10.83	2.56e−008	−11.6	4	6f::DRG1:OAL:GPS:B:THR200:HG1 6f::DRG1:NAG:GPS:B:ARG202:HE 6f::DRG1:OAL:GPS:B: ARG201:HN 6f::DRG1:OAO:GPS:A:ARG201:HH22
6g	−9.25	−11.01	1.65e−007	−10.5	2	6g::DRG1:OAL:GPS:B:GLY183:O 6g::DRG1:OAO:GPS:B:ARG202:HH22
6h	−9.07	−9.9	2.24E−007	−10.32	4	6h::DRG1:OAO:GPS:B:ARG217:HH22 6h::DRG1:OAQ:GPS:B:MET184:O 6h::DRG1:OAQ:GPS:A:ARG10:HH11 6h::DRG1:OAO:GPS:B:ARG216:HH12
6i	−9.71	−10.98	7.64e−008	1.56	5	6i::DRG1:OAX:GPS:B: MET184:O 6i::DRG1:OAX:GPS:A:ARG10:HH11 6i::DRG1:OAO:GPS:B:ARG216:HH22 6i::DRG1:OAO:GPS:B:ARG216:HH12 6i::DRG1:OAO:GPS:B:ARG217:HH22
Streptomycin	−1.54	−5.72	0.07	−4.34	4	SM::DRG1:H67:GPS:A:ALA8:O SM::DRG1:H42:GPS:A:THR67:OG1 SM::DRG1:OBH:GPS:A:ARG217:HE SM::DRG1:H7B:GPS:B:ASP11:OD2
Nystatin	2400	2410	0	2400	8	NY:: DRG1:OCE:GPS:B:ARG10:HH11 NY:: DRG1:OCK:GPS:A:ARG216:HH21 NY:: DRG1:OCE:GPS:A:MET184:HN NY:: DRG1:OAF:GPS:A:ARG202:HH12 NY:: DRG1:HCS:GPS:B:GLU14:OE2 NY:: DRG1:OCH:GPS:A:THR200:HG1 NY:: DRG1:OBY:GPS:A:ARG216:HH11 NY:: DRG1:OCK:GPS:A:ARG217:HH22

synthase, which catalyzes a complex reaction involving ammonia transfer from L-glutamine to Fru-6-P, followed by isomerization of the formed fructosamine-6-phosphate to glucosamine-6-phosphate. Hence, this study has provedthat molecule **6i** to be one of the potent antibacterial and antifungal agent.

Conclusion

Starting from aniline, novel substituted quinoline derivatives (**6a**–**i**) were synthesized with moderate to excellent yields. The obtained products were thoroughly characterized by spectral techniques. The crystal and molecular structure of the two compounds (**6a** and **6e**) have been determined. Weak interactions and supramolecular assembly, involving several hydrogen bonding interactions of different functional groups have been demonstrated. It is observed that the crystal structure of the two compounds is stabilized by strong intermolecular C—H···N and C—H···O hydrogen bonds. Additionally the supramolecular assembly is consolidated by special type of Cg–Cg (π-ring) interaction. The structure analysis of these compounds provides an insight into the correlation between molecular structures and intermolecular interactions in compounds for drug development. Some of these derivatives were found effective against tested organisms. This provides further scope for evaluation of this class of compounds for other biological activities and also in particular with data pertaining to structure–activity relationships. It is also expected that the drugs synthesized using the above would pave a new way for the planning, designing and synthesis of next generation drugs.

Acknowledgements

JPJ acknowledges the NSF-MRI program (Grant No. CHE-1039027) for funds to purchase the X-ray diffractometer. THS

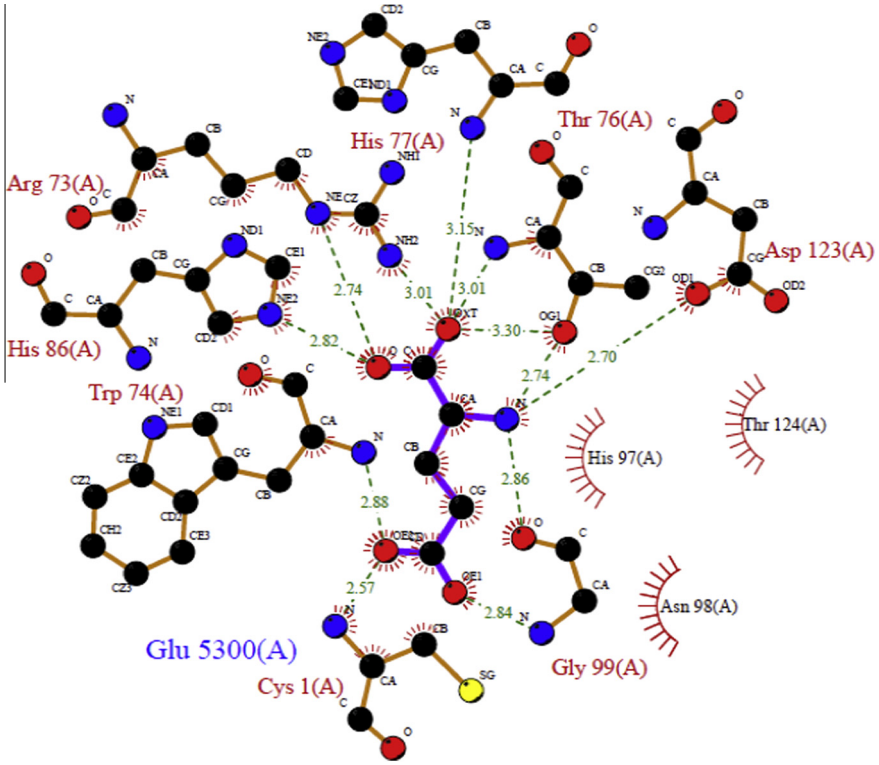


Fig. 6. Interacting amino acids as predicted from the ligplot.

acknowledges the NMRC, IISc, Bangalore for providing ^{1}H NMR and ^{13}C NMR spectra.

Appendix A. Supplementary material

CCDC 972576 and 972577 contains the supplementary crystallographic data for $C_{12}H_{10}NO_2Cl$ and $C_{13}H_{12}ClNO_2$. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336 033; or email: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2014.04.009.

References

[1] M. Foley, L. Tilley, Pharmacol. Ther. 79 (1998) 55–87.
[2] V.K. Gupta, A. Mittal, V. Gajbe, J. Colloid Interface Sci. 284 (2005) 89–98.
[3] H.M. Grandin, S.M. Tadayyon, W.N. Lennard, K. Griffiths, L.L. Coatsworth, P.R. Norton, Z.D. Popovic, H. Aziz, N.X. Hu, Org. Electron. 4 (2003). pp. 19–14.
[4] X. Zhao, X. Zhan, Chem. Soc. Rev. 40 (2011) 3728–3743.
[5] O. Bilker, V. Lindo, M. Panico, A.E. Etiene, T. Paxton, A. Dell, M. Rogers, R.E. Sinden, H.R. Morris, Nature 392 (1998) 289–292.
[6] G. Roma, M.D. Braccio, G. Grossi, F. Mattioli, H. Ghia, Eur. J. Med. Chem. 35 (2000) 1021–1035.
[7] Y.L. Chen, K.C. Fang, J.Y. Sheu, S.L. Hsu, C.C. Tzeng, J. Med. Chem. 44 (2000) 2374–2377.
[8] K.C. Fang, Y.L. Chen, J.Y. Sheu, T.C. Wang, C.C. Tzeng, J. Med. Chem. 43 (2000) 3809–3812.
[9] J. Chevalier, S. Atifi, A. Eyraud, A. Mahamoud, J. Barbe, J. Med. Chem. 44 (2001) 4023–4026.
[10] L.T. Phan, T. Jian, Z. Chen, Y.Q. Qiu, Z. Wang, T. Beach, A. Polemeropoulos, J. Med. Chem. 47 (2004) 2965–2968.
[11] S.J. Benkovic, S.J. Baker, M.R.K. Alley, Y.H. Woo, Y.K. Zhang, T. Akama, W. Mao, J. Baboval, P.T.R. Rajagopalan, M. Wall, L.S. Kahng, A. Tavassoli, L. Shapiro, J. Med. Chem. 48 (2005) 7468–7476.
[12] K. MajerzManiecka, B. Oleksyn, R. Musiol, B. Podeszwa, Polanski, J. Abstracts Papers (2005) 20–23.
[13] L.Y. Vargas, M.V. Castelli, V.V. Kouznetsov, J.M. Urbina, S.N. Lopez, M. Sortino, R.D. Enriz, J.C. Ribas, S. Zacchino, Bioorg. Med. Chem. 11 (2003) 1531–1550.
[14] M. Singh, M.P. Singh, S.Y. Ablordeppey, Drug Dev. Ind. Pharm. 22 (1996) 377–381.
[15] L. Dassonneville, A. Lansiaux, A. Wattelet, N. Wattez, C. Mahieu, S. Van Miert, L. Pieters, C. Bailly, Eur. J. Pharmacol. 409 (2000) 9–18.
[16] L. Dassonneville, K. Bonjean, M.C. De Pauw-Gillet, P. Colson, C. Houssier, J. Quetin-Leclercq, L. Angenot, S.Y. Ablordeppey, Bioorg. Med. Chem. 10 (2002) 1337–1346.
[17] C. Bailly, Biochemistry 38 (1999) 7719–7726.
[18] C. Bailly, W. Laine, B. Baldeyrou, M.C. De Pauw-Gillet, P. Colson, C. Houssier, K. Cimanga, S.V. Miert, A.J. Vlietinck, L. Pieters, Anti-Cancer Drug Des. 15 (2000) 191–201.
[19] B. Kunze, G. Hofle, H. Reichenbach, J. Antibiot. 40 (1987) 258–265.
[20] J. Adams, C. Giam, Environ. Sci. Technol. 18 (1984) 391–394.
[21] N.M. Shavaleev, H. Adams, J. Best, R. Edge, S. Navaratnam, J.A. Weinstein, Inorg. Chem. 45 (2006) 9410–9415.
[22] P.J. Bindu, K.M. Mahadevan, N.D. Satyanarayan, T.R. RavikumarNaik, Bioorg. Med. Chem. Lett. 22 (2012) 898–900.
[23] Charnsak Thongsornkleeb, Charnsak Thongsornkleeb, Somsak Ruchirawata, Tanita Gettongsonga, Org. Biomol. Chem. 11 (2013) 1463.
[24] Norio Sakai, Kosuke Tamura, Kazuyori Shimamura, Reiko Ikeda, Takeo Konakahara, Org. Lett. 14 (2012) 836–839.
[25] Younes Laras, Vincent Hugues, Yogesh Chandrasekaran, Mireille Blanchard Desce, Francine C. Acher, Nicolas Pietrancosta, J. Org. Chem. 77 (2012) 8294–8302.
[26] Ram Shankar Upadhayaya, Popat Shinde, A. SandipKadam, N. AmitBawane, Y. Aftab, Sayyed, A. RamakantKardile, N. Pallavi, Gitay, V. Santosh, Lahore, S. Shailesh Dixit, Andras Foldesi, Jyoti Chattopadhyaya, Eur. J. Med. Chem. 46 (2011) 1306–1324.
[27] Neha Sharma, Mrityunjaya Asthana, Durgesh Nandini, R.P. Singh, M. RadheySingh, Tetrahedron 69 (2013) 1822–1829.
[28] V. Krishnakumar, Fazlur-Rahman Nawaz Khan, Badal Kumar Mandal, Sukanya Mitta, Ramu Dhasamandha, Vindhya NanuGovindan, Res. Chem. Intermed. 38 (2012) 1819–1826.
[29] Ulrich Abel, Angela Hansen, Falko Ernst Wolter, Bioern Krueger, Valerians Kauss, Jevgenijs Rozhkovs, Valentina Semenihina, Irena Piskunova, Juris Pelss, PCT Int. Appl. (2012) 2012164085.
[30] M. SimonaCeccarelli, Aurelia Conte, Holger Kuehne, Bernd Kuhn, Werner Neidhart, Sander Ulrike Obst, Markus Rudolph, PCT Int. Appl. (2013) 2013064465.
[31] W. Donald Landry, Shixian Deng, Ottavio Aranico, Joie Fiorito, Andrew Wasmuth, PCT Int. Appl. (2013) 2013109738.
[32] Jae In Lee, Bull. Korean Chem. Soc. 33 (2012) 1375–1378.
[33] Wu Yiran, Zheng Chen, Ying Liu, Yu Lanlan, Lu Zhou, Suijia Yang, Luhua Lai, Bioorg. Med. Chem. 19 (2011) 3361–3366.
[34] M.J. Davis, O.D. Iancu, F. Acher, B.M. Stewart, M.A. Eiwaz, R.M. Duvoisin, J. Raber, J. Org. Chem. 77 (2012) 8294–8302.

[35] K. Pong, Exp. Opin. Biol. Therapy. 3 (2003) 127–139.
[36] B. Sandhya, S. Manoharan, G. SirishaLavanya, Ch. RatnaManmohan, Indian J. Sci. Technol. 3 (2010) 83–86.
[37] D. Anderson, Mutation Res. 350 (1999) 103–108.
[38] K. Balakumar, S. RamanathanKumaresan, R. Suresh, Indian J. Sci. Technol. 3 (2010) 322–327.
[39] M.A. Anagnostopoulou, P. Kefalas, V.P. Papageorgiou, A.N. Assimepoulou, D. Boskou, Food Chem. 94 (2006) 19–25.
[40] U. Carounanidy, R. Satyanarayanan, A. Velmurugan, Indian J. Dent. Res. 18 (2007) 152–156.
[41] M.L. Cohen, Science 257 (1992) 1050–1055.
[42] G.F. NascimentoGislene, L. Juliana, C.F. Paulo, L.S. Giuliana, Braz. J. Microbiol. 31 (2000) 247–256.
[43] W.M. Rockey, A.H. Elcock, J. Med. Chem. 48 (2005) 4138–4152.
[44] E. Ramesh, T.K. SreeVidhya, R. Raghunathan, Tetrahedron Lett. 49 (2008) 2810.
[45] M. Kidwai, N. Negi, Monatsh. Chem. 128 (1997) 85.
[46] B.W. Cohen, D.E. Polyansky, R. Zong, H. Zhou, T. Ouk, D.E. Cabelli, R.P. Thummel, E. Fujita, Inorg. Chem. 49 (2010) 8034.
[47] P. Rajakumar, R. Raja, Tetrahedron Lett. 51 (2010) 4365.
[48] P. Venkatesan, S.J. Sumathi, Heterocycl. Chem. 47 (2010) 81.
[49] A. Srivastava, R.M. Singh, Indian J. Chem. 44B (2005) 1868.
[50] M. Nyerges, A. Pinter, A. Viranyi, B. Gabor, L. To ke, Tetrahedron 61 (2005) 8199.
[51] V.S.H. Krishnan, P.K. Dubey, S.S. Rao, V. Aparna, Indian J. Heterocycl. Chem. 13 (2003) 11.
[52] V.S.H. Krishnan, P.K. Dubey, S.S. Rao, P.V.P. Reddy, Indian J. Heterocycl. Chem. 13 (2003) 5.
[53] P.K. Dubey, S.S. Rao, P.V.P. Reddy, Indian J. Heterocycl. Chem. 9 (2003) 411.
[54] K. Mogilaiah, N.V. Reddy, R.B. Rao, Indian J. Heterocycl. Chem. 11 (2002) 253.
[55] M.M. Ali, S. Sana, R.K.C. Tasneem, P.K. Saiprakash, Synth. Commun. 32 (2002) 1351.
[56] S.M. Roopan, F.R.N. Khan, Arkivoc (2009) 161–169.
[57] B. Zeynizadeh, T. Behyar, Chem. Soc. Jpn. 78 (2005) 307.
[58] N.S. Narashimhan, N.M. Sunder, R. Ammanamanchi, B.D. Bonde, J. Am. Chem. Soc. 112 (1990) 4431.
[59] B. Bhat, A.P. Bhaduri, Indian J. Chem. 23B (1984) 33.
[60] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, J. Appl. Cryst. 42 (2009) 339.
[61] Superflip, J. Appl. Cryst. 40 (2007) 786.
[62] G.M. Shelxl, Sheldrick, Acta Cryst. A64 (2008) 112.
[63] P. Sithisarn, R. Supabphol, W. Gritsanapan, J. Ethnopharmacol. 99 (2005) 109–112.
[64] R. Nair, T. Kalariya, S. Chanda, Turkish J. Biol. 29 (2005) 1–47.
[65] C.H. Collins, P.M. Lyne, J.M. Grange, Microbiol. Methods, 6th ed. (1989) 410.
[66] M.S. Ali-Shtayeh, R. M Yaghmour, Y.R. Faidi, K. Salem, M.A. Al-Nuri, J. Ethnopharmacol. 60 (1998) 265–271.
[67] R.K. Pundir, P. Jain, J. Pharm. Res. 3 (2010) 506–510.
[68] A.K. Ghose, G.M. Crippen, J. Chem. Inf. Comput. Sci. 27 (1987) 21–35.
[69] T.A. Binkowski, S. Naghibzadeg, J. Liang, Nucleic Acid Res. 31 (2003) 3352–3355.
[70] J. Gasteiger, M. Marsili, Tetrahedron 36 (1980) 3219–3288.
[71] G.M. Morris, D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew, A.J. Olson, J. Comput. Chem. 19 (1998) 1639–1662.
[72] S.S. Praveen Kumar Darsi, K.S. Nagamani, B. Rama Devi, A. Naidu, P.K. Dubey, Der. Pharma. Chem. 3 (2011) 35–38.
[73] F. Korodi, Z. Szabo, Heterocycl. Commun. 1 (1995) 297–306.
[74] F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, R. Taylor, J. Chem. Soc. Perkin Trans. 2 (1987). pp. S1–19.
[75] M.M. Cowan, Clin. Microbiol. Rev. 12 (2002) 564–582.