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ORIGINAL PAPER

# Synthesis and an Evaluation of Molecular Conformation and Crystal Packing in Two Substituted 4-Phenylquinolines

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**Abstract** The title compounds, namely Methyl 2-methyl-4 -phenylquinoline-3-carboxylate (I), $C_{18}H_{15}NO_2$, and (2E)-3-(3,4-dimethoxyphenyl)-1-(2-methyl-4 -phenylquinolin-3-yl)prop-2-en-1-one (II), $C_{27}H_{23}NO_3$, comprising of the phenyl ring, exhibit differences in conformational behaviour with respect to the plane of the quinoline fragment. (I) contains the methyl ester moiety whereas (II) contains the chalcone fragment, consisting of a double bond and phenyl group containing dimethoxy groups as substituents. The dihedral angles between the phenyl group and the quinoline ring is 82.77 (7)° in (I), and 79.02 (8)° in (II) respectively. It is the weak C–H···O=C H-bond and C–H···$\pi$ interactions which dictate packing of molecules in (I). In (II), it is C–H···N and C–H···$\pi$, involving the dimethoxy ring, which controls packing of molecules in the crystal lattice. In addition, $\pi$···$\pi$ aromatic stacking interactions involving the quinoline fragment is present in all the molecules.

**Keywords** Phenylquinolines · Molecular conformation · Intermolecular interactions · Hydrogen bonds

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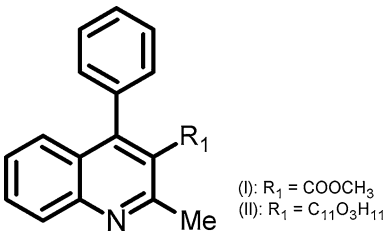
## Introduction

The treatment of different diseases today involves the screening of small organic molecules for their biological activity which finds subsequent applications as compounds for therapeutic purposes. One such dangerous disease is malaria, which affects half of the world population. People living in tropical and subtropical areas are most affected by this disease (e.g. [1, 2]). A large number of molecules namely chloroquine, mefloquine, primaquine and amodiaquine [3] are used for the prevention and treatment of malaria. All these contain the quinoline ring, a functional group which has been most effective for malarial therapy. This nucleus is found in many organic molecules, either synthetic or natural and exhibiting a wide range of pharmacological activities, such as anti-viral, anti-cancer, anti-bacterial, anti-fungal, and anti-inflammatory activities (e.g. [4–7]) and are valuable reagents for the synthesis of nano and mesostructures with enhanced electronic and photonic properties [8].

In view of clinical applications of these classes of compounds, single crystal structure determinations and the subsequent supramolecular perspectives have been delineated in detail in substituted chloroquinine [9] and related biologically active phosphate compounds exhibiting anti-malarial activity [10]. A majority of these structures contain a molecular skeleton corresponding to the 4-quinoline moiety. The molecular skeleton is divided into three parts, namely the quinoline ring, the phenyl ring and most of the crystallographic investigations involve varying substituents on the quinoline fragment (Scheme 1).

In the current article, we report the crystal and molecular structure of 4-phenyl-quinoline containing methyl and methyl ester moiety in (I), and the chalcone fragment containing dimethoxy groups in (II). The chalcone




**Scheme 1** Molecular structure of the investigated compounds

functionality is also biologically very potent and exhibits broad range of biological activites. All the related functions along with crystallographic investigations involving chalcones are summarized in an article [20]. It is of interest to investigate structurally two highly relevant biological fragments in the same molecule for their molecular geometry and packing preferences in crystalline solids. In the light of the above mentioned statements, we present in this article, the pertinent structural highlights obtained from crystallographic investigations performed on compounds (I)–(II).

## Experimental

### Synthesis

The title compound was synthesized by the following procedures.

(I): A mixture of 2-aminobenzophenone (1.9 g, 0.01 M) and methyacetoacetate (1.2 g, 0.01 M) with 0.15 ml concentrated HCl taken in a beaker was subjected to microwave irradiation (240 W) for about 6 min. After completion of the reaction (TLC), the reaction mixture was washed with saturated $NaHCO_3$ solution (10 ml), dried, washed with petroleum ether and re crystallized with chloroform (Yield: 74%; M.P: 408–411 K; IR data (in $cm^{-1}$): 1703 (C=O stretching frequency), 1198 (C–O stretching frequency of O–$CH_3$ group). The observed crystals were colourless and block morphology was observed.

(II): A mixture of 3-acetyl-2-methyl-4-phenylquinoline (2.6 g 0.01 M) and 3,4-dimethoxybenzaldehyde (1.66 g, 0.01 M) and a catalytic amount of KOH in distilled ethanol was stirred for about 24 h, the resulting mixture was concentrated to remove ethanol then poured on to ice and neutralized with dilute acetic acid. The resultant solid was filtered, dried and purified by column chromatography using 1:1 mixture of ethyl acetate and petroleum ether and recrystallized from acetone (Yield: 66%; M.P: 412–413 K: IR data (in $cm^{-1}$): 1638 (stretching frequency of C=O for $\alpha$, $\beta$- unsaturated ketone), 1588 (C=C stretching frequency for $\alpha$, $\beta$- unsaturated ketone). Block shaped colorless crystals were obtained.

## Data Collection and Refinement

Single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer using graphite monochromated $MoK_\alpha$ ($\lambda = 0.7107$ Å) radiation at 290(2) K and the intensities were measured using $\omega$ scan with a scan width of 0.3°. A total of 606 frames per set were collected in different settings of $\phi$ ($\phi = 0°$, 90° and 180° if the system is monoclinic; $\phi = 0°$, 90°, 180°) keeping the sample to detector distance of 6.03 cm. The data were reduced by SAINTPLUS [11] and an empirical absorption correction was applied using the package SADABS [11] available in the Bruker software package. All the crystal structures were solved by direct methods using SIR92 [12] and refined by full matrix least squares method using SHELXL97 [13] present in the program suite WinGX (Version 1.63.04a) [14]. All the H-atoms were positioned geometrically and refined using a riding model with d(C–H) = 0.93/0.96 Å, Uiso = 1.2–1.5 Ueq (C) for aromatic, methyl hydrogens. ORTEP diagrams of all the compounds were generated using ORTEP32 [15] and packing diagrams were generated using CAMERON [16] available in the WinGX program suite and MERCURY [17]. Geometrical calculations were done using PARST95 [18] and PLATON [19]. Crystallographic data (excluding structure factors) for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, Nos. CCDC-856600 (I), and CCDC-856601 (II). Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, e-mail:deposit@ccdc.cam.ac.uk, or www.ccdc.cam.ac.uk.

## Results and Discussion

Table 1 highlights the relevant crystallographic data. Figures 1 and 2 depicts the atom-numbering scheme for all the compounds of current investigation. Figures 3 and 4 depicts the corresponding packing diagrams of all the molecules for (I) and (II) in the unit cell.

In (I), the torsion angle C18–C9–C8–C10, between the ester moiety and methyl fragment is 2.1 (2)°. The ester group makes a torsion of 74.5 (2)° with the quinoline moiety. The crystal structure is stabilized by weak, yet highly directional C–H···O hydrogen bonds (involving H15) and C–H···$\pi$ interactions (involving H12) of the 4-phenyl ring forming dimeric motifs in the solid state (Fig. 3; Table 2). There exists $\pi$···$\pi$ interactions between the quinoline motifs, the stacking distance being 3.8671 (19) Å. In (II), the torsion C17–C9–C8–C10 is −2.4 (3)° between the chalcone fragment and the methyl group. The configuration of the C18=C19 double bond [1.329 (2) Å] is

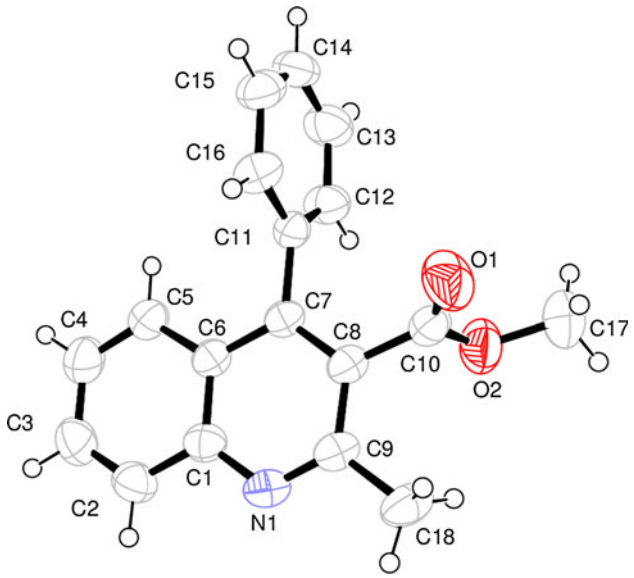



**Fig. 1** The structure of (I) showing the atom-numbering scheme. Displacement *ellipsoids* are drawn at 50% probability level

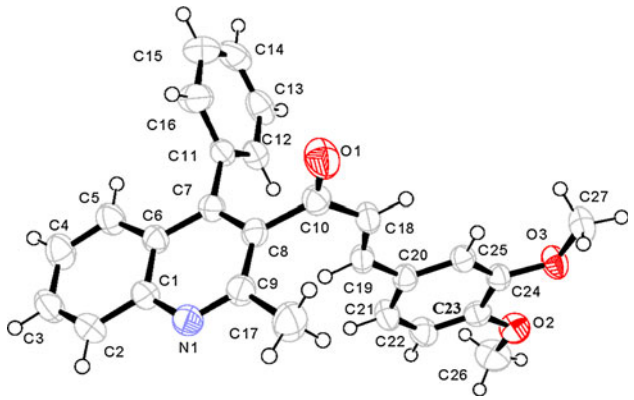



**Fig. 2** The structure of (II) showing the atom-numbering scheme. Displacement *ellipsoids* are drawn at 50% probability level

*E* and the chalcone residue is approximately perpendicular to the quinolinyl residue, the torsion angle C7–C8–C10–C18 being −93.91 (19)°. The packing is dictated by weak but linear C–H···N hydrogen bonds, involving H14, forming chains along the crystallographic [110] direction along with C–H···$\pi$ interactions, involving H21 and the 4-phenyl ring, forming chains along *a* axis (Fig. 4; Table 2). Aromatic $\pi$···$\pi$ interactions between the quinoline motifs is also present, the stacking distance being 3.7991 (10) Å. Such interactions involving the $\pi$-rings are of significance in crystal packing and have been investigated both from an experimental and theoretical perspective [21, 22].

A related compound, namely, (2E, 4E)-1-(6-Chloro-2-methyl-4-phenyl-3-quinolyl)-5-phenylpenta-2,4-dien-1-one, has also been investigated [23]. It contains a double bond in conjugation with the C18=C19 double bond in (II)

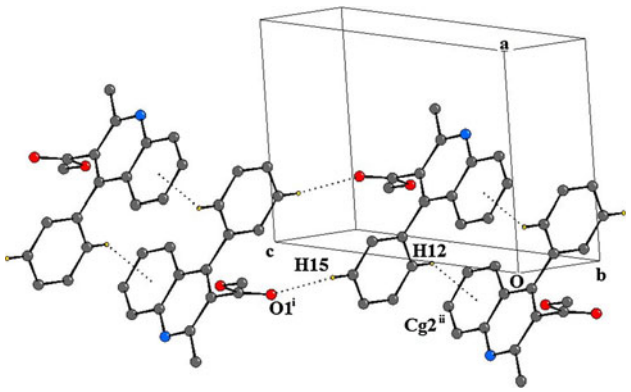



**Fig. 3** Packing diagram in (I) depicting C–H···O and C–H···$\pi$ interaction dimers. The molecules at '*i*' and '*ii*' have the symmetry code (−x, −y + 1, −z + 2) and (−x + 2, −y, −z + 1). Cg2 depicts the center of gravity of the six-membered phenyl ring C1/C6. Hydrogen atoms not taking part in the interaction have been omitted for clarity

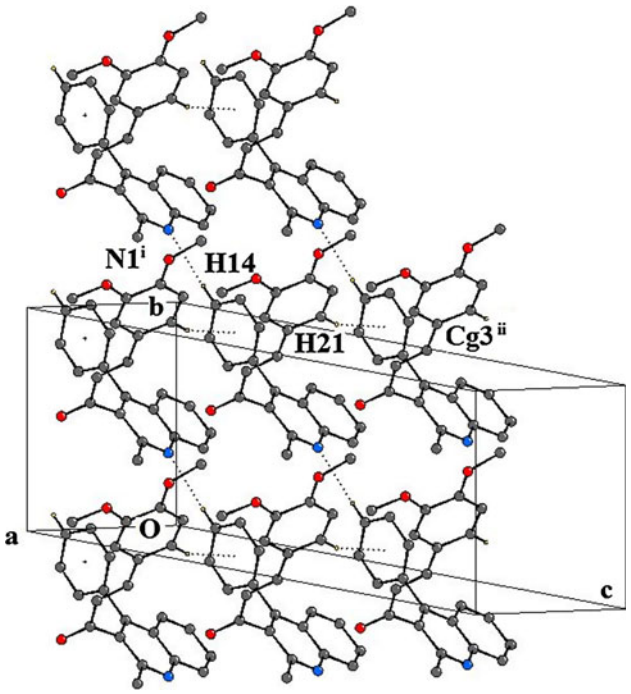



**Fig. 4** Packing diagram in (II) depicting C–H···N and C–H···$\pi$ interactions. Molecules at i and ii are located at (x + 1, y + 1, z) and (x + 1, y, z). Cg3 depicts the center of gravity of the six-membered phenyl ring C11/C16. Hydrogen atoms not taking part in the interaction have been omitted for clarity

along with absence of bis-methoxy group followed by presence of a chlorine atom in the 6-position. The quinoline ring forms a dihedral angle of 62.53(5)° with the benzene ring. The torsion angle between the keto group of the chalcone fragment and methyl group is approximately 5.2°. Structurally related compounds containing the chalcone moiety along with different functional groups have also been recently reported in the literature [24–30].

**Table 1** Crystal data, data collection and structure refinement

| Compound | I | II |
|---|---|---|
| Formula | $C_{18}H_{15}NO_2$ | $C_{27}H_{23}NO_3$ |
| Size of crystal (mm) | 0.2 × 0.2 × 0.15 | 0.3 × 0.2 × 0.10 |
| Formula weight | 277.31 | 409.46 |
| Crystal System | Triclinic | Monoclinic |
| Space group | *P*-1 | $P2_1/n$ |
| *T*(K) | 292(2) | 292(2) |
| *a*(Å) | 8.9412 (2) | 6.2373(2) |
| *b*(Å) | 9.2235 (2) | 8.5718(3) |
| *c*(Å) | 10.7903 (2) | 2162.36(12) |
| α (°), β(°), γ(°), *V* (Å$^3$) | 73.026 (1)°, 66.519 (1)°, 63.341 (1)°, 722.43 (3) | 90, 90.961(2), 90, 2162.36(12) |
| *Z* | 2 | 4 |
| Dx (g cm$^{-3}$) | 1.275 | 1.258 |
| F(000) | 292 | 864 |
| $\mu$(mm$^{-1}$) | 0.083 | 0.082 |
| $\theta$ range (°) | 2.5, 26.0 | 2.0, 26.0 |
| *h*, *k*, *l* range | (−11, 11), (−11, 11), (−13, 13) | (−7, 7), (−10, 10), (−49, 49) |
| Reflections Collected | 11521 | 34511 |
| Unique Reflections($R_{int}$) | 2798 (0.0164) | 4261(0.0505) |
| Observed Reflections (with $I > 2\sigma(I)$) | 2208 | 3057 |
| Number of Parameters | 192 | 283 |
| R_obs, R_all | 0.0432, 0.0568 | 0.0450, 0.0702 |
| $wR_2$_obs, $wR_2$_all | 0.1121, 0.1248 | 0.1043, 0.1183 |
| G.O.F | 1.031 | 1.017 |
| $\Delta\rho_{max,\ min}$ (e Å$^{-3}$) | 0.168, −0.141 | 0.205, −0.168 |

**Table 2** List of H-bonding geometry

| | D | H | A | D–H | H···A | D···A | D–H···A | Symmetry code |
|---|---|---|---|---|---|---|---|---|
| I | C15 | H15 | O1 | 0.93 | 2.81 | 3.733(2) | 173 | (−x, −y + 1, −z + 2) |
| | C12 | H12 | Cg2 | 0.93 | 2.85 | 3.648(2) | 144 | (−x + 2, −y, −z + 1). |
| II | C14 | H14 | N1 | 0.93 | 2.60 | 3.518(3) | 171 | (x + 1, y + 1, z) |
| | C21 | H21 | Cg3 | 0.93 | 2.74 | 3.837(2) | 162 | (x + 1, y, z) |

A search of the Cambridge Structural Database (CSD, Version 5.31, November 2009) performed for searching the structures containing the 6-chloro-4-phenyl-quinoline moiety, gave three hits. The compounds are 6-Chloro-10-phenyl-1,2,3,4-tetrahydroacridine [31], 2,3-Trimethylene-4-phenyl-6-chloroquinoline [32], and 2-Chloro-12-phenyl-6,7,8,9,10,11-hexahydrocycloocta(b)quinoline [33] containing cyclohexene, cyclopentene and cyclooctene ring in the 2,3-position of the quinoline ring. The torsion angles between the phenyl and the quinoline ring are 73°, 62° and 77° in the three related compounds, respectively. This is because of the increased steric interactions between the hydrogens on the carbon atom (part of the cyclic ring system) with the hydrogens ortho to the carbon atom of the phenyl ring. In case of the five membered ring, the ring size being smaller results in decreased steric interactions and hence greater flexibility with respect to rotation about the C–C bond connected to the phenyl ring. These values are also comparable with those reported for compounds (I)-(II). The determination of the molecular conformation for compounds reported in references [22] and [23] essentially has the same chalcone moiety [with different substitutions] and phenyl ring [no substitution], wherein the dihedral angles between the phenyl ring with the

quinoline ring vary between 54° and 88°. The differences essentially stem from the different intermolecular interactions which govern crystal packing when a different functional group is introduced on a fixed molecular scaffold. In fact this forms the basis of the problem of crystal engineering wherein the importance of weak interactions in dictating molecular conformation in organic solids is realised. The chalcone moiety is close to being orthogonal [dihedral angle varies from 70° to 105°] with respect to the plane of the quinoline ring, indicating free rotation about the C–C bond to minimize steric interaction of the methyl hydrogens with the hydrogen atoms of the conjugated double bond of the chalcone moiety.

In conclusion, it is of interest to investigate molecular conformation, strong and weak intermolecular H-bonds along with Van der Waals interactions operating between different functional groups present in an organic solid. Such studies provide suitable pointers to the fact that all the above-mentioned factors are significant to decide the overall packing of molecules in the crystal lattice. These are again of importance during docking processes (protein–ligand interactions) as both are events of molecular recognition.

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