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Novel chalcones derived from 2-chloro-3-formyl-6-methylquinoline

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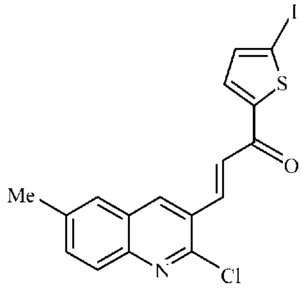
Molecules of (*E*)-3-(2-chloro-6-methylquinolin-3-yl)-1-(5-iodo-2-thienyl)prop-2-en-1-one, $C_{17}H_{11}ClINOS$, (I), and (*E*)-3-(2-chloro-6-methylquinolin-3-yl)-1-(5-methyl-2-furyl)prop-2-en-1-one, $C_{18}H_{14}ClNO_2$, (II), adopt conformations slightly twisted from coplanarity. Both structures are devoid of classical hydrogen bonds. However, nonclassical C—H$\cdots$O/N interactions [with C$\cdots$O = 3.146 (5) Å and C$\cdots$N = 3.487 (3) Å] link the molecules into chains extended along the *b* axis in (I) and form dimers with an $R_2^2(8)$ motif in (II). The structural analysis of these compounds provides an insight into the correlation between molecular structures and intermolecular interactions in compounds for drug development.

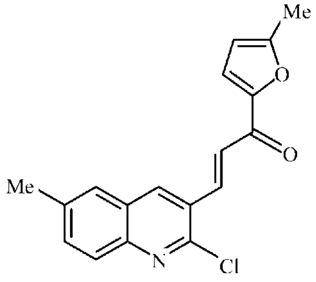
Comment

Chalcones, α,β-unsaturated ketones, constitute an important group of natural products that serve as precursors for the synthesis of different classes of flavonoids (Lin *et al.*, 2002), pyrimidines, imidazoles (Varga *et al.*, 2003) and 2-pyrazolines (Lévai, 2005). Some possess anticancer (Prabhavat & Ghiya, 1998), antimalarial (Wu *et al.*, 2002), antitubercular, antitumour, anti-inflammatory, antiviral and antimicrobial activities (Opletalova & Sedivy, 1999). In order to correlate their molecular structures and intermolecular interactions with their biological manifestations, we have synthesised and determined the crystal structures of two new quinoline-based chalcones, namely (*E*)-3-(2-chloro-6-methylquinolin-3-yl)-1-(5-iodo-2-thienyl)prop-2-en-1-one, (I), and (*E*)-3-(2-chloro-6-methylquinolin-3-yl)-1-(5-methyl-2-furyl)prop-2-en-1-one, (II). A series of similar chalcones are under investigation for biological activity.

The molecule of (I) (Fig. 1) has the mean planes of the 2-chloro-6-methylquinoline and (5-iodo-2-thienyl)prop-2-en-1-one moieties inclined at 12.87 (6)°, resulting in a slightly twisted conformation. The maximum deviations of atoms Cl1 and C11 from these planes are 0.047 (2) and 0.048 (3) Å, respectively. The structure, without classical hydrogen bonds, contains intermolecular C—H$\cdots$O interactions involving thiophene atom H15 and carbonyl atom O1 of a neighbouring molecule (Table 1), linking the molecules into chains along the (010) direction (Fig. 2). These chains are oriented in opposite directions, with the thiophene (S1/C13–C16) and benzene (C1–C6) ring centroids separated by 3.649 (3) Å (perpendicular distance = 3.40 Å), indicating weak π–π interactions.



(I)



(II)

In (II) (Fig. 3), the mean planes of the 2-chloro-6-methylquinoline and (5-methyl-2-furyl)prop-2-en-1-one moieties are inclined at 11.11 (5)° in a slightly twisted conformation similar to (I). The maximum deviations of atoms C3 and C10 from these planes are 0.039 (2) and 0.077 (2) Å, respectively. The structure of (II) is also without classical hydrogen bonds, but, unlike the case for (I), there is an intermolecular C—H$\cdots$N interaction between atom H2 bonded to atom C2 and atom N1 of the quinoline ring system of a neighbouring molecule (Table 2), which links the molecules into dimers (Fig. 4), forming eight-membered rings with an $R_2^2(8)$ motif (Bernstein *et al.*, 1994). Unlike the π–π interactions observed in (I), the furan rings of the symmetry-related molecules in (II) lie parallel to each other, with a distance of 3.798 (2) Å between the ring centroids. Moreover, a methyl H atom bonded to C18

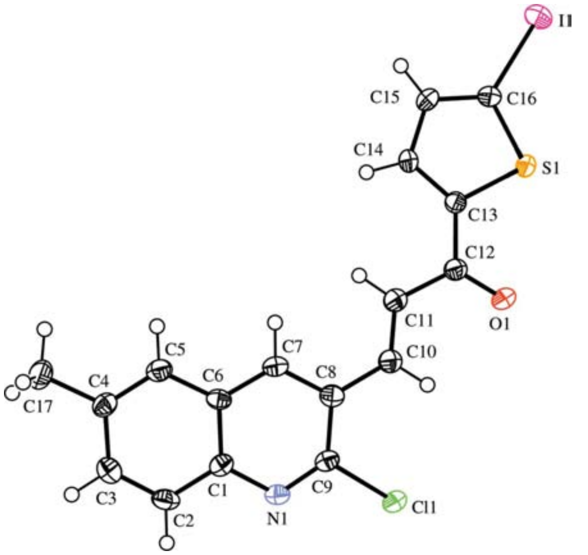


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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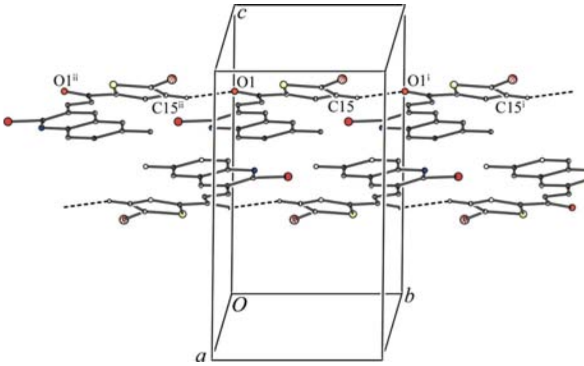

Figure 2
Intermolecular interactions in the unit cell of (I), depicted as dashed lines. Only H atoms involved in interactions have been included. [Symmetry codes: (i) $x, y + 1, z$; (ii) $x, y - 1, z$.]

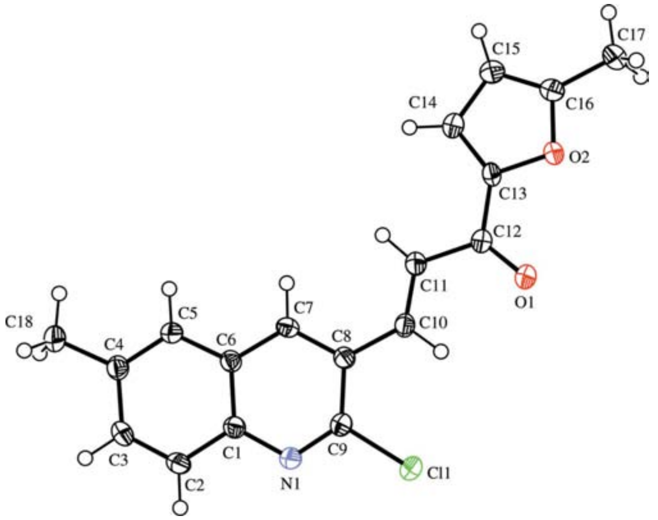

Figure 3
The molecular structure of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

is oriented towards the heterocyclic ring (N1/C1/C6–C9), with a perpendicular distance H18*A*$\cdots$*Cg* of 2.82 Å (*Cg* is the centroid of the ring).

The bond distances and angles in both structures are mostly in agreement with expected values (Orpen *et al.*, 1994). The C12—C13—C14 angles have been widened to 131.1 (4) and 134.34 (18)° for (I) and (II), respectively, as reported in a large number of thiophene derivatives [Cambridge Structural Database (CSD), Version 5.29; Allen, 2002]. The C9—Cl1 bond distances in (I) and (II) of 1.765 (4) and 1.751 (2) Å, respectively, lie within the range (1.722–1.782 Å) of corresponding distances in 22 structures in the CSD containing the 2-chloroquinoline fragment, excluding those involved in metal complexes. The Cl1—C9—N1 and Cl1—C9—C8 angles of 114.4 (3) and 118.2 (3)° in (I), and 114.52 (14) and 119.20 (15)° in (II), respectively, also lie within the ranges of the corresponding angles in related structures (112.0–118.2 and 116.4–121.2°, respectively). Furthermore, the C8—C10—C11 angles are significantly different in (I) and (II), at 125.5 (4) and 128.25 (18)°, respectively. The remaining angles lie within narrow ranges in both structures. A search of the CSD for 2-chloroquinoline groups containing a C atom attached at position 3 revealed only the following structures: 2-chloro-3-(chloromethyl)quinoline (CSD refcode ATEDEI; Lu *et al.*, 2003), 1,5-bis(4-chlorophenyl)-3-(2-chloroquinolin-3-yl)pentane-1,5-dione (MAZZET; Insuasty *et al.*, 2006), (*S*)-2-(2-chloroquinolin-3-yl)-2-[(*S*)-α-methylbenzylamino]acetonitrile (MEHDAF; Belfaitah *et al.*, 2006) and 2-chloro-3-(β-nitrovinyl)quinoline (QAMNAU; Palani *et al.*, 2004).

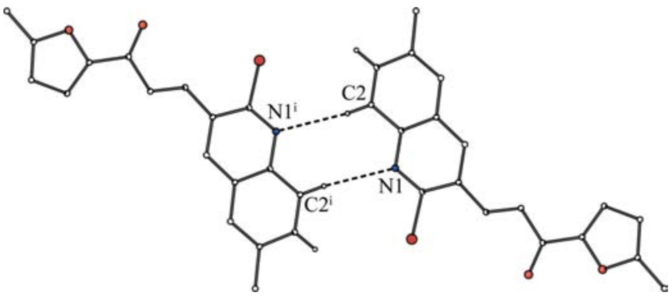

Figure 4
Intermolecular interactions in the dimeric unit of (II), depicted as dashed lines. Only H atoms involved in interactions have been included. [Symmetry code: (i) $-x, y, -z - \frac{1}{2}$.]

Experimental

The precursor 2-chloro-3-formyl-6-methylquinoline was prepared according to a literature procedure (Meth-Cohn *et al.*, 1981). A mixture of 2-chloro-3-formyl-6-methylquinoline (2.055 g, 10 mmol) and 5-iodo-2-acetylthiophene (2.5207 g, 10 mmol) or 2-acetyl-5-methylfuran (1.2414 g, 10 mmol) in methanol (50 ml) was stirred at room temperature, followed by dropwise addition of aqueous NaOH (4 ml, 10%). The stirring was continued for 2 h and the reaction mixture was then kept at 273 K for 24 h. Subsequently, it was poured into ice-cold water (200 ml). The precipitates were collected by filtration and washed with cold water followed by cold MeOH. The resulting chalcones were recrystallized from $CHCl_3$ to obtain colourless solid crystalline products, *viz.* (I) and (II). Analysis for (I): m.p. 457–458 K; IR (neat, ν_{max}, cm^{-1}): C=O 1648 (*s*), C=C 1596 (*m*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (*s*, 3H, CH_3), 7.36 (*d*, 1H, $H_{4'}$, J = 3.92 Hz), 7.37 (*d*, 1H, H_α, J = 15.54 Hz), 7.50 (*d*, 1H, $H_{3'}$, J = 3.98 Hz), 7.59 (*dd*, 1H, H_7, J = 8.70 Hz), 7.62 (*s*, 1H, H_5), 7.90 (*d*, 1H, H_8, J = 8.54 Hz), 8.20 (*d*, 1H, H_β, J = 15.60 Hz), 8.35 (*s*, 1H, H_4); yield: 3.17 g, 7.21 mmol (72%). Analysis for (II): m.p. 445–447 K; IR (neat, ν_{max}, cm^{-1}): C=O 1654 (*s*), C=C 1594 (*m*); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (*s*, 3H, CH_3), 2.54 (*s*, 3H, CH_3), 6.24 (*dd*, 1H, $H_{4'}$, J = 3.39 Hz), 7.29 (*d*, 1H, $H_{3'}$, J = 3.45 Hz), 7.45 (*d*, 1H, H_α, J = 15.70 Hz), 7.58 (*dd*, 1H, H_7, J = 8.60 Hz), 7.63 (*s*, 1H, H_5), 7.90 (*d*, 1H, H_8, J = 8.58 Hz), 8.22 (*d*, 1H, H_β, J = 15.79 Hz), 8.38 (*s*, 1H, H_4); yield: 2.56 g, 8.21 mmol (82%).

Compound (I)

Crystal data

$C_{17}H_{11}ClINOS$
M_r = 439.68
Monoclinic, $P2_1/c$
a = 17.112 (6) Å
b = 7.636 (3) Å
c = 13.174 (5) Å
β = 111.29 (2)°
V = 1603.9 (10) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 2.29 mm^{-1}
T = 173 (2) K
0.26 × 0.07 × 0.06 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
$T_{\min} = 0.587$, $T_{\max} = 0.875$
6042 measured reflections
3652 independent reflections
2663 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.036$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.097$
$S = 1.03$
3652 reflections
200 parameters
H-atom parameters constrained
$\Delta\rho_{\max} = 0.52$ e Å^{-3}
$\Delta\rho_{\min} = -0.63$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
C15—H15···O1$^{\rm i}$	0.95	2.22	3.146 (5)	163

Symmetry code: (i) $x, y+1, z$.

Compound (II)

Crystal data

$C_{18}H_{14}ClNO_2$
$M_r = 311.75$
Monoclinic, $C2/c$
$a = 36.228$ (10) Å
$b = 7.372$ (3) Å
$c = 11.214$ (5) Å
$\beta = 99.70$ (2)°
$V = 2952$ (2) Å^3
$Z = 8$
Mo $K\alpha$ radiation
$\mu = 0.27$ mm^{-1}
$T = 173$ (2) K
0.22 × 0.20 × 0.07 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
$T_{\min} = 0.944$, $T_{\max} = 0.982$
6103 measured reflections
3355 independent reflections
2405 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.038$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.110$
$S = 1.01$
3355 reflections
200 parameters
H-atom parameters constrained
$\Delta\rho_{\max} = 0.25$ e Å^{-3}
$\Delta\rho_{\min} = -0.24$ e Å^{-3}

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···N1$^{\rm i}$	0.95	2.61	3.487 (3)	154

Symmetry code: (i) $-x, y, -z-\frac{1}{2}$.

For both structures, H atoms were included in the refinements in geometrically idealized positions, with aryl and methyl C—H distances of 0.95 and 0.98 Å, respectively, and $U_{\rm iso}({\rm H}) = 1.2U_{\rm eq}({\rm C})$. The H atoms bonded to methyl atom C17 in (II) were equally disordered over six sites. The final difference maps were free of chemically significant features.

For both compounds, data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SAPI91* (Fan, 1991); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG3168). Services for accessing these data are described at the back of the journal.

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