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Synthesis, structure and *in vitro* cytotoxicity testing of some 1,3,4-oxadiazoline derivatives from 2-hydroxy-5-iodobenzoic acid

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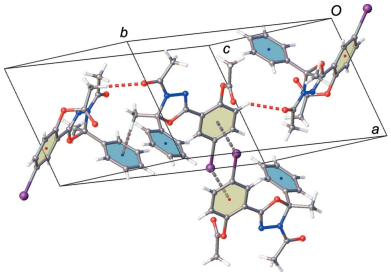
Supporting information: this article has supporting information at journals.iucr.org/c

The syntheses of nine new 5-iodosalicylic acid-based 1,3,4-oxadiazoline derivatives starting from methyl salicylate are described. These compounds are 2-[4-acetyl-5-methyl-5-(3-nitrophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6a**), 2-[4-acetyl-5-methyl-5-(4-nitrophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6b**), 2-(4-acetyl-5-methyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-iodophenyl acetate, $C_{19}H_{17}IN_2O_4$ (**6c**), 2-[4-acetyl-5-(4-fluorophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate, $C_{19}H_{16}FIN_2O_4$ (**6d**), 2-[4-acetyl-5-(4-chlorophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate, $C_{19}H_{16}ClIN_2O_4$ (**6e**), 2-[4-acetyl-5-(3-bromophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6f**), 2-[4-acetyl-5-(4-bromophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6g**), 2-[4-acetyl-5-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6h**) and 2-[5-(4-acetamidophenyl)-4-acetyl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6i**). The compounds were characterized by mass, ^{1}H NMR and ^{13}C NMR spectroscopies. Single-crystal X-ray diffraction studies were also carried out for **6c**, **6d** and **6e**. Compounds **6c** and **6d** are isomorphous, with the 1,3,4-oxadiazoline ring having an envelope conformation, where the disubstituted C atom is the flap. The packing is determined by C—H···O, C—H···π and I···π interactions. For **6e**, the 1,3,4-oxadiazoline ring is almost planar. In the packing, Cl···π interactions are observed, while the I atom is not involved in short interactions. Compounds **6d**, **6e**, **6f** and **6h** show good inhibiting abilities on the human cancer cell lines KB and Hep-G2, with IC_{50} values of 0.9–4.5 μM.

1. Introduction

Derivatives of 1,3,4-oxadiazoline show a broad spectrum of biological activity, including antibacterial (Joshi *et al.*, 2008; Suresh Kumar *et al.*, 2010; Mohitea & Bhaskar, 2011; Hamdi *et al.*, 2011; Naveena *et al.*, 2011; Kotb *et al.*, 2009), antifungal (Mohitea & Bhaskar, 2011; Naveena *et al.*, 2011; Kotb *et al.*, 2009), antitubercular (Joshi *et al.*, 2008; Suresh Kumar *et al.*, 2010), anti-inflammatory (Rajak *et al.*, 2007; Sahoo *et al.*, 2014), antioxidant (Hamdi *et al.*, 2011; Sahoo *et al.*, 2014; Manojkumar *et al.*, 2009; Fadda *et al.*, 2011) and antitumour activities (Kotb *et al.*, 2009; Manojkumar *et al.*, 2009; Fadda *et al.*, 2011). Furthermore, it is well documented that 1,3,4-oxadiazoline derivatives display a pronounced effect on the



enzyme tyrosinase (El Sadek *et al.*, 2013) or chitin biosynthesis (Ke *et al.*, 2009).

On the other hand, salicylic acid and structurally related compounds were found to possess antimicrobial (Khiati *et al.*, 2007; Sarshira *et al.*, 2016), analgesic and antitumour activities (Pattan *et al.*, 2009; Vejselova & Kutlu, 2015; Huang *et al.*, 2018). Research on the antibacterial properties of salicylic acid derivatives with respect to viscose fabrics shows that the antibacterial activity of salicylic acid and its derivatives are in the following order: 5-bromosalicylic acid > salicylic acid > 5-chlorosalicylic acid > 4-chlorosalicylic acid (Kantouch *et al.*, 2013). However, iodinated derivatives of salicylic acid have not been studied much. Recently, a series of salicylic acid-based 1,3,4-oxadiazole derivatives were synthesized and some of them showed good antitumour activities, with IC_{50} values ranging from 31.19 to 57.21 μ*M* (Murty *et al.*, 2014). As a continuation of our research work exploring potent bioactive 5-iodosalicylic acid-based oxadiazole derivatives (Cong *et al.*, 2012), nine new 2-(4-acetyl-5-aryl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-iodophenyl acetate compounds were synthesized (see Scheme 1) and their antitumour activities evaluated against KB and Hep-G2.

2. Experimental

All chemicals were obtained from commercial sources and used without further purification. The melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on an FT–IR Shimadzu 8400-S. NMR spectra were measured on a Bruker Avance 500 MHz in dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal reference. All NMR spectra are available in the supporting information. Mass spectra were recorded on a Bruker micrOTOF-Q 10187 mass spectrometer.

2.1. Synthesis and crystallization

Methyl salicylate (**2**), methyl 2-hydroxy-5-iodobenzoate (**3**) and 2-hydroxy-5-iodobenzohydrazide (**4**) were synthesized according to previously reported methods (Cong *et al.*, 2012).

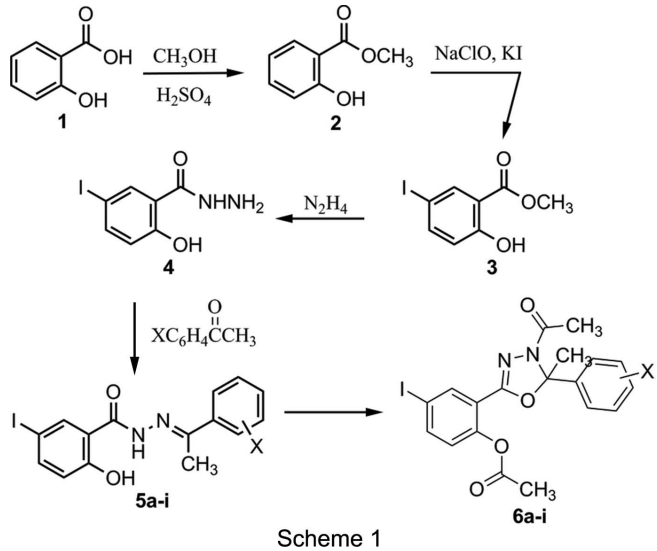
Methyl salicylate (**2**): liquid; b.p. 494–495 K, yield 73%.

Methyl 2-hydroxy-5-iodobenzoate (methyl 5-iodosalicylate) (**3**): white needles, m.p. 347–348 K, yield 85%; IR (ν, cm^{-1}): 3156, 3080, 2949, 1676, 1604, 527.

2-Hydroxy-5-iodobenzohydrazide (**4**): white needles, m.p. 451 K, yield 79%; IR (ν, cm^{-1}): 3405, 3322, 1626, 1574, 529; ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.41 (1H, *br*, OH), 10.12 (1H, *br*, NH), 8.12 (1H, *d*, ^4J = 2.0, ArH), 7.65 (1H, *dd*, ^3J = 9.0, ^4J = 2.0, ArH), 6.75 (1H, *d*, ^3J = 9.0, ArH), 4.80 (2H, *br*, NH_2); ^{13}C NMR: 166.1 (CO), 158.9, 141.3, 135.5, 119.9, 117.4, 80.5.

2.1.1. General procedure for the synthesis of *N*′-(1-arylethylidene)-2-hydroxy-5-iodobenzohydrazide compounds (5a–5i). Equimolar quantities of hydrazide **4** and a substituted acetophenone (*X* = 3-NO_2, 4-NO_2, 4-H, 4-F, 4-Cl, 3-Br, 4-Br, 4-CH_3 and 4-NH_2) were refluxed in ethanol for 2 h. The reaction mixture was cooled to room temperature and the precipitate was filtered off and crystallized from dioxane or a mixture of DMF and water to give the corresponding products **5a**–**5i**.

2-Hydroxy-5-iodo-*N*′-[1-(3-nitrophenyl)ethylidene]benzohydrazide (**5a**): yield 88%, m.p. 508–509 K; IR (ν, cm^{-1}): 3217 (OH, N—H), 1636, 1559 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.07 (1H, *br*, OH), 11.42 (1H, *s*, NH), 8.65 (1H, *s*, Ar-H), 8.29 (2H, *m*, Ar-H), 8.22 (1H, *d*, ^4J = 2.0, Ar-H), 7.77 (1H, *dd*, $^3J_1$ = $^3J_1$ = 8.0, ArH), 7.73 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, ArH), 6.89 (1H, *d*, ^3J = 8.5, ArH), 2.42 (3H, *s*, CH_3); ^{13}C NMR: δ 161.2 (C═O), 156.4, 150.8, 148.5, 142.0, 140.0, 139.1, 134.2, 133.3, 130.6, 124.4, 121.2, 121.1, 120.1, 82.3, 14.4; MS: *m*/*z* 447.9718 (*M* + Na)$^+$, calculated for $C_{16}H_{15}NO_7SNa$: 447.9770; MS: *m*/*z* 425.9924 (*M* + H)$^+$, calculation for $C_{15}H_{13}IN_3O_4$: *M* = 425.9951 a.u.



Scheme 1

2-Hydroxy-5-iodo-*N*′-[1-(4-nitrophenyl)ethylidene]benzohydrazide (**5b**): yield 82%, m.p. 532–533 K; IR (ν, cm^{-1}): 3094 (OH, N—H), 1643, 1535 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.07 (1H, *br*, OH), 11.43 (1H, *s*, NH), 8.31 (2H, *d*, ^3J = 8.5, Ar-H), 8.22 (1H, *d*, ^4J = 2.0, Ar-H), 8.12 (2H, *d*, ^3J = 8.5, Ar-H), 7.74 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, ArH), 6.89 (1H, *d*, ^3J = 8.5, ArH), 2.40 (3H, *s*, CH_3); ^{13}C NMR: δ 161.2 (C═O), 156.7, 150.8, 148.1, 144.4, 142.1, 139.1, 128.1, 124.1, 121.1, 120.1, 82.3, 14.3; MS: *m*/*z* 447.9718 (*M* + Na)$^+$, calculation for $C_{15}H_{12}IN_3NaO_4$: *M* = 447.9770 a.u.

2-Hydroxy-5-iodo-*N*′-(1-phenylethylidene)benzohydrazide (**5c**): yield 84%, m.p. 452–453 K; IR (ν, cm^{-1}): 3295, 3040 (OH, N—H), 2917 (Csp^3—H), 1643, 1566 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.06 (1H, *br*, OH), 11.29 (1H, *s*, NH), 8.23 (1H, *d*, ^4J = 2.0, Ar-H), 7.87 (2H, *m*, Ar-H), 7.73 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, ArH), 7.46 (3H, *m*, Ar-H), 6.89 (1H, *d*, ^3J = 8.5, ArH), 2.35 (3H, *s*, CH_3); ^{13}C NMR: δ 160.6 (C═O), 156.3, 152.9, 141.4, 138.5, 137.8, 129.5, 128.4, 126.5, 120.6, 119.6, 81.8, 13.9; MS: *m*/*z* 380.9992 (*M* + H)$^+$, calculation for $C_{15}H_{14}IN_2O_2$: *M* = 381.0100 a.u.

***N*′-[1-(4-Fluorophenyl)ethylidene]-2-hydroxy-5-iodobenzohydrazide** (**5d**): yield 77%, m.p. 507–508 K; IR (ν, cm^{-1}): 3295, 3102 (OH, N—H), 2930 (Csp^3—H), 1643, 1605 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.04 (1H, *br*, OH), 11.27 (1H, *s*, NH), 8.22 (1H, *d*, ^4J = 2.0, Ar-H), 7.92 (2H, *dd*, ^3J = 8.5, $^4J_{H\text{-}F}$ = 5.5, Ar-H), 7.72 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, ArH), 7.29 (2H, *dd*, ^3J = 8.5, $^3J_{H\text{-}F}$ = 8.5, Ar-H), 6.88 (1H, *d*, ^3J = 8.5, ArH),

2.34 (3H, *s*, CH_3); ^{13}C NMR: δ 162.9 (*d*, $^1J_{C\text{-}F}$ = 982.0), 160.6 (C═O), 156.2, 151.9, 141.4, 138.5, 134.3 (*d*, $^4J_{C\text{-}F}$ = 11.0), 128.7 (*d*, $^3J_{C\text{-}F}$ = 33.5), 120.6, 119.6, 115.3 (*d*, $^2J_{C\text{-}F}$ = 86.0), 81.7, 13.9; MS: *m*/*z* 399.0007 $(M + H)^+$, calculation for $C_{15}H_{13}FIN_2O_2$: *M* = 399.0006 a.u.

***N′*-[1-(4-Chlorophenyl)ethylidene]-2-hydroxy-5-iodobenzohydrazide (5e)**: yield 85%, m.p. 542–543 K; IR (ν, cm^{-1}): 3287, 3088 (OH, N—H), 2932 (C*sp*^{3}—H), 1643, 1550 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.05 (1H, *br*, OH), 11.30 (1H, *s*, NH), 8.22 (1H, *s*, Ar-H), 7.89 (2H, *d*, ^3J = 8.0, Ar-H), 7.73 (1H, *dd*, ^3J = 8.5, ^4J = 1.5, ArH), 7.53 (2H, *d*, ^3J = 8.0, Ar-H), 6.89 (1H, *d*, ^3J = 8.5, ArH), 2.33 (3H, *s*, CH_3); ^{13}C NMR: δ 160.6 (C═O), 156.2, 151.5, 141.4, 138.5, 136.6, 134.2, 128.4, 128.2, 120.6, 119.6, 81.8, 13.7; MS: *m*/*z* 414.9674 $(M + H)^+$, calculation for $C_{15}H_{13}ClIN_2O_2$: *M* = 414.9710 a.u.

***N′*-[1-(3-Bromophenyl)ethylidene]-2-hydroxy-5-iodobenzohydrazide (5f)**: yield 82%, m.p. 546–547 K; IR (ν, cm^{-1}): 3412, 3071 (OH, N—H), 1644, 1556 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.01 (1H, *br*, OH), 11.30 (1H, *s*, NH), 8.21 (1H, *d*, ^4J = 1.5, Ar-H), 8.03 (1H, *s*, Ar-H), 7.83 (1H, *d*, ^3J = 8.0, Ar-H), 7.71 (1H, *dd*, ^3J = 8.0, ^4J = 1.5, ArH), 7.63 (1H, *d*, ^3J = 8.0, Ar-H), 7.42 (1H, *dd*, $^3J_1$ = $^3J_2$ = 8.0, ArH), 6.87 (1H, *d*, ^3J = 8.5, ArH), 2.32 (3H, *s*, CH_3); ^{13}C NMR: δ 161.2 (C═O), 156.7, 151.6, 141.9, 140.6, 139.0, 132.6, 131.1, 129.3, 126.1, 122.4, 121.1, 120.1, 82.2, 14.3; MS: *m*/*z* 414.9674 $(M + H)^+$, calculation for $C_{15}H_{12}BrIN_2O_2$: *M* = 457.9127 a.u.

***N′*-[1-(4-Bromophenyl)ethylidene]-2-hydroxy-5-iodobenzohydrazide (5g)**: yield 86%, m.p. 555–556 K; IR (ν, cm^{-1}): 3285, 3034 (OH, N—H), 2938 (C*sp*^{3}—H), 1647, 1593 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.03 (1H, *br*, OH), 11.30 (1H, *s*, NH), 8.22 (1H, *d*, ^4J = 2.0, Ar-H), 7.82 (2H, *d*, ^3J = 8.5, Ar-H), 7.72 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, ArH), 7.66 (2H, *d*, ^3J = 8.5, Ar-H), 6.89 (1H, *d*, ^3J = 8.5, ArH), 2.33 (3H, *s*, CH_3); ^{13}C NMR: δ 161.1 (C═O), 156.7, 152.1, 141.9, 139.0, 137.5, 131.9, 129.0, 123.5, 121.1, 120.1, 82.3, 14.2; MS: *m*/*z* 458.8999 $(M + H)^+$, calculation for $C_{15}H_{13}BrIN_2O_2$: *M* = 458.9205 a.u.

2-Hydroxy-5-iodo-*N′*-[1-(4-methylphenyl)ethylidene]benzohydrazide (5h): yield 76%, m.p. 501–502 K; IR (ν, cm^{-1}): 3279, 3035 (OH, N—H), 2940 (C*sp*^{3}—H), 1645, 1600 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 12.04 (1H, *br*, OH), 11.24 (1H, *s*, NH), 8.23 (1H, *d*, ^4J = 2.0, Ar-H), 7.76 (2H, *d*, ^3J = 8.5, Ar-H), 7.72 (1H, *dd*, ^3J = 8.5, ^4J = 2.5, ArH), 7.26 (2H, *d*, ^3J = 8.5, Ar-H), 6.88 (1H, *d*, ^3J = 8.5, ArH), 2.32 (3H, *s*, Ar-CH_3), 2.31 (3H, *s*, CH_3); ^{13}C NMR: δ 160.6 (C═O), 156.3, 152.9, 141.3, 139.2, 138.5, 135.0, 129.0, 126.4, 120.6, 119.6, 81.7, 20.9, 13.8; MS: *m*/*z* 395.0247 $(M + H)^+$, calculation for $C_{16}H_{16}IN_2O_2$: *M* = 395.0256 a.u.

***N′*-[1-(4-Aminophenyl)ethylidene]-2-hydroxy-5-iodobenzohydrazide (5i)**: yield 78%, m.p. 515–516 K; IR (ν, cm^{-1}): 3440, 3298, 3201 (OH, N—H), 2932 (C*sp*^{3}—H), 1634, 1577 (C═O, C═N); ^{1}H NMR (δ in ppm and *J* in Hz): δ 11.11 (1H, *s*, NH), 8.23 (1H, *s*, Ar-H), 7.70 (1H, *d*, ^3J = 8.5, ArH), 7.59 (2H, *d*, ^3J = 8.5, Ar-H), 6.86 (1H, *d*, ^3J = 8.5, ArH), 6.59 (2H, *d*, ^3J = 8.5, Ar-H), 5.55 (2H, *br*, NH_2), 2.22 (3H, *s*, CH_3); ^{13}C NMR: δ 161.1 (C═O), 157.0, 154.8, 150.9, 141.6, 138.7, 128.3, 125.2, 121.0, 120.1, 113.7, 82.0, 14.1; MS: *m*/*z* 396.0069 $(M + H)^+$, calculation for $C_{15}H_{15}IN_3O_2$: *M* = 396.0209 a.u.

2.1.2. General procedure for the synthesis of 2-(4-acetyl-5-aryl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-iodophenyl acetate compounds (6a–6i). A mixture of *N*-substituted hydrazides (**5a**–**5i**) (5 mmol) and acetic anhydride (10 ml) was taken into a 100 ml round-bottomed flask. The mixture was refluxed for 4 h. After cooling to room temperature, the reaction mixture was poured into ice cold water. The precipitate obtained was filtered off and crystallized from a mixture of ethanol and water to give the corresponding products. For compounds **6c**, **6d** and **6e**, the crystals were suitable for X-ray diffraction.

2-[4-Acetyl-5-methyl-5-(3-nitrophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (6a): IR (ν, cm^{-1}): 3079 (C*sp*^{2}—H), 2986 (C*sp*^{3}—H), 1751, 1659 (C═O), 1589 (C═N, C═C); ^{1}H NMR (δ in ppm and *J* in Hz): δ 8.30 (2H, *m*, Ar-H), 8.10 (1H, *d*, ^4J = 2.0, Ar-H), 8.00 (2H, *m*, Ar-H), 7.77 (1H, *t*, ^3J = 8.0, Ar-H), 7.16 (1H, *d*, ^3J = 8.5, Ar-H), 2.26 (9H, *m*, 3 × CH_3); ^{13}C NMR: δ 169.2, 166.9, 149.4, 148.7, 148.4, 142.1, 141.0, 137.3, 132.9, 130.9, 127.0, 124.8, 121.1, 120.0, 99.4, 91.7, 22.7, 22.6, 21.2; MS: *m*/*z* 531.9991 $(M + Na)^+$; calculation for $C_{19}H_{16}IN_3NaO_6$: *M* = 532.0008 a.u.

2-[4-Acetyl-5-methyl-5-(4-nitrophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (6b): IR (ν, cm^{-1}): 3055 (C*sp*^{2}—H), 2940 (C*sp*^{3}—H), 1759, 1667 (C═O), 1605 (C═N, C═C); ^{1}H NMR (δ in ppm and *J* in Hz): δ 8.29 (2H, *d*, ^3J = 9.0, Ar-H), 8.08 (1H, *d*, ^4J = 2.0, Ar-H), 8.00 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, Ar-H), 7.83 (2H, *d*, ^3J = 8.5, Ar-H), 7.15 (1H, *d*, ^3J = 8.5, Ar-H), 2.26 (6H, *m*, 2 × CH_3), 2.23 (3H, *s*, CH_3); ^{13}C NMR: δ 169.2, 166.8, 149.4, 148.7, 148.4, 145.4, 142.1, 137.3, 128.0, 127.0, 124.2, 120.0, 99.3, 91.7, 22.7, 22.6, 21.2; MS: *m*/*z* 531.9991 $(M + Na)^+$; calculation for $C_{19}H_{16}IN_3NaO_6$: *M* = 531.9981 a.u.

2-(4-Acetyl-5-methyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-iodophenyl acetate (6c): IR (ν, cm^{-1}): 2950 (C*sp*^{3}—H), 1767, 1667 (C═O); ^{1}H NMR (δ in ppm and *J* in Hz): δ 8.05 (1H, *d*, ^4J = 2.0, Ar-H), 7.98 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, Ar-H), 7.51 (2H, *d*, ^3J = 7.0, Ar-H), 7.44 (3H, *m*, Ar-H), 7.13 (1H, *d*, ^3J = 8.5, Ar-H), 2.25 (3H, *s*, CH_3), 2.24 (3H, *s*, CH_3), 2.20 (3H, *s*, CH_3); ^{13}C NMR: δ 169.2, 166.5, 149.3, 148.7, 141.9, 139.1, 137.2, 129.8, 129.0, 126.9, 126.1, 120.3, 100.4, 91.7, 22.8, 22.7, 21.1; MS: *m*/*z* 487.0126 $(M + Na)^+$; calculation for $C_{19}H_{17}IN_2NaO_4$: 487.0131 a.u.

2-[4-Acetyl-5-(4-fluorophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (6d): IR (ν, cm^{-1}): 3094 (C*sp*^{2}—H), 2940 (C*sp*^{3}—H), 1759, 1659 (C═O), 1605 (C═N, C═C); ^{1}H NMR (δ in ppm and *J* in Hz): δ 8.07 (1H, *s*, Ar-H), 7.98 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, Ar-H), 7.57 (2H, *m*, Ar-H), 7.26 (2H, *dd*, ^3J = 8.0, Ar-H), 7.16 (1H, $^3J_{H\text{-}H}$ = $^3J_{H\text{-}F}$ = 9.0, Ar-H), 7.13 (1H, *d*, ^3J = 8.5, Ar-H), 2.25 (3H, *s*, CH_3), 2.24 (3H, *s*, CH_3), 2.19 (3H, *s*, CH_3); ^{13}C NMR: δ 169.1, 166.5, 163.9, 161.9, (149.3, 148.7), 141.9, 137.3, (135.477, 135.453), (128.739, 128.670), 126.9, 120.3, (115.922, 115.749), 99.9, 91.6, 22.8, 22.7, 21.1; MS: *m*/*z* 505.0044 $(M + Na)^+$; calculation for $C_{19}H_{16}FIN_2NaO_4$: *M* = 505.0036 a.u.

2-[4-Acetyl-5-(4-chlorophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (6e): IR (ν, cm^{-1}): 3094 (C*sp*^{2}—H), 1767, 1667 (C═O), 1597 (C═N, C═C); ^{1}H NMR (δ in ppm and *J* in Hz): δ 8.06 (1H, *d*, ^4J = 2.0, Ar-H), 7.98 (1H,

Table 1
Experimental details.

	6c	6d	6e
Crystal data			
Chemical formula	$C_{19}H_{17}IN_2O_4$	$C_{19}H_{16}FIN_2O_4$	$C_{19}H_{16}ClIN_2O_4$
M_r	464.24	482.24	498.69
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$
Temperature (K)	100	100	100
a, b, c (Å)	8.837 (1), 20.056 (1), 11.015 (1)	9.1241 (4), 20.0980 (9), 10.7456 (5)	11.703 (2), 22.037 (4), 7.4073 (12)
β (°)	110.18 (1)	110.224 (2)	92.888 (8)
V (Å^3)	1832.4 (3)	1849.00 (15)	1907.9 (5)
Z	4	4	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	1.77	1.77	1.85
Crystal size (mm)	0.42 × 0.20 × 0.16	0.60 × 0.37 × 0.29	0.22 × 0.12 × 0.12
Data collection			
Diffractometer	Bruker APEXII CCD	Bruker APEXII CCD	Bruker APEXII CCD
Absorption correction	Multi-scan (*SADABS*; Bruker, 2014)	Multi-scan (*SADABS*; Bruker, 2014)	Multi-scan (*SADABS*; Bruker, 2014)
T_{min}, T_{max}	0.627, 0.747	0.610, 0.746	0.640, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	54289, 5600, 4994	52242, 4033, 3703	62840, 4387, 3863
R_{int}	0.029	0.048	0.042
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.714	0.639	0.650
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.022, 0.050, 1.05	0.020, 0.047, 1.06	0.021, 0.051, 1.04
No. of reflections	5600	4033	4387
No. of parameters	238	247	247
H-atom treatment	H-atom parameters constrained	H-atom parameters constrained	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.97, −0.59	0.56, −0.32	0.40, −0.66

Computer programs: *APEX2* (Bruker, 2014), *SAINT* (Bruker, 2013), *SHELXS97* (Sheldrick, 2008), *SHELXT* (Sheldrick, 2015*a*), *SHELXL2014* (Sheldrick, 2015*b*) and *OLEX2* (Dolomanov *et al.*, 2009).

dd, ^3J = 8.5, ^4J = 2.0, Ar-H), 7.50 (2H, *d*, ^3J = 8.5, Ar-H), 7.51 (2H, *d*, ^3J = 8.5, Ar-H), 7.14 (1H, *d*, ^3J = 8.5, Ar-H), 2.25 (3H, *s*, CH_3), 2.24 (3H, *s*, CH_3), 2.18 (3H, *s*, CH_3); ^{13}C NMR: δ 168.7, 166.1, 148.8, 148.2, 141.5, 137.5, 136.8, 134.1, 128.6, 127.8, 126.5, 119.7, 99.3, 91.2, 22.2, 22.1, 20.7; MS: *m*/*z* 520.9743 (*M* + Na)$^+$; calculation for $C_{19}H_{16}ClIN_2NaO_4$: 520.9741 a.u.

2-[4-Acetyl-5-(3-bromophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6f**): IR (ν, cm^{-1}): 3071 (Csp^2—H), 2932 (Csp^3—H), 1767, 1651 (C═O); ^{1}H NMR (δ in ppm and *J* in Hz): δ 8.07 (1H, *d*, ^4J = 2.0, Ar-H), 7.98 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, Ar-H), 7.70 (1H, *s*, Ar-H), 7.64 (1H, *t*, $^3J_1$ = $^3J_2$ = 7.0, Ar-H), 7.52 (1H, *d*, ^3J = 7.5, Ar-H), 7.41 (1H, *m*, Ar-H), 2.25 (6H, *m*, 2 × CH_3), 2.18 (3H, *s*, CH_3); ^{13}C NMR: δ 169.1, 166.7, 149.4, 148.7, 142.0, 141.5, 137.3, 132.8, 131.3, 129.0, 126.9, 125.4, 122.3, 120.2, 99.6, 91.7, 22.7, 22.6, 21.1; MS: *m*/*z* 564.9230 (*M* + Na)$^+$; calculation for $C_{19}H_{16}BrIN_2NaO_4$: *M* = 564.9236 a.u.

2-[4-Acetyl-5-(4-bromophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6g**): IR (ν, cm^{-1}): 3094 (Csp^2—H), 1767, 1667 (C═O), 1620, 1589 (C═N, C═C); ^{1}H NMR (δ in ppm and *J* in Hz): δ 8.05 (1H, *d*, ^4J = 2.0, Ar-H), 7.98 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, Ar-H), 7.65 (2H, *d*, ^3J = 8.5, Ar-H), 7.47 (2H, *d*, ^3J = 8.0, Ar-H), 7.14 (1H, *d*, ^3J = 8.5, Ar-H), 2.25 (3H, *s*, CH_3), 2.23 (3H, *s*, CH_3), 2.17 (3H, *s*, CH_3); ^{13}C NMR: δ 169.1, 166.6, 149.3, 148.7, 142.0, 138.4, 137.3, 132.0, 128.6, 127.0, 123.3, 120.2, 99.8, 91.7, 22.7, 22.6, 21.1; MS: *m*/*z* 564.9244 (*M* + Na)$^+$; calculation for $C_{19}H_{16}BrIN_2NaO_4$: *M* = 564.9236 a.u.

2-[4-Acetyl-5-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6h**): IR (ν, cm^{-1}): 3009 (Csp^2—H), 2924 (Csp^3—H), 1767, 1667 (C═O), 1620 (C═N, C═C); ^{1}H NMR (δ in ppm and *J* in Hz): δ 8.04 (1H, *d*, ^4J = 2.0, Ar-H), 7.97 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, Ar-H), 7.39 (2H, *d*, ^3J = 8.0, Ar-H), 7.24 (2H, *d*, ^3J = 8.0, Ar-H), 7.13 (1H, *d*, ^3J = 8.5, Ar-H), 2.32 (3H, *s*, CH_3), 2.24 (3H, *s*, CH_3), 2.23 (3H, *s*, CH_3), 2.18 (3H, *s*, CH_3); ^{13}C NMR: δ 169.1, 166.3, 149.3, 148.7, 141.8, 139.3, 137.2, 136.2, 129.5, 126.9, 126.1, 120.4, 100.4, 91.6, 22.8, 22.7, 21.2, 21.1; MS: *m*/*z* 501.0261 (*M* + Na)$^+$; calculation for $C_{20}H_{19}IN_2NaO_4$: *M* = 501.0267 a.u.

2-[5-(4-Acetamidophenyl)-4-acetyl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (**6i**): IR (ν, cm^{-1}): 3320 (NH), 3070 (Csp^2—H), 2934 (Csp^3—H), 1763, 1655 (C═O), 1601 (C═N, C═C); ^{1}H NMR (δ in ppm and *J* in Hz): δ 10.08 (1H, *s*, NH), 8.03 (1H, *d*, ^4J = 2.0, Ar-H), 7.97 (1H, *dd*, ^3J = 8.5, ^4J = 2.0, Ar-H), 7.62 (2H, *d*, ^3J = 7.0, Ar-H), 7.41 (2H, *d*, ^3J = 7.0, Ar-H), 7.13 (1H, *d*, ^3J = 8.5, Ar-H), 2.24 (3H, *s*, CH_3), 2.23 (3H, *s*, CH_3), 2.18 (3H, *s*, CH_3), 2.16 (3H, *s*, CH_3), 2.05 (3H, *s*, CH_3); ^{13}C NMR: δ 172.7, 169.2, 166.6, 149.3, 148.7, 141.9, 140.8, 137.3, 133.6, 129.7, 126.9, 120.4, 119.2, 100.3, 91.6, 27.2, 24.5, 22.8, 22.7, 21.1; MS: *m*/*z* 544.0173 (*M* + Na)$^+$; calculation for $C_{21}H_{20}IN_3NaO_5$: *M* = 544.0345 a.u.

2.2. Structure solution and refinement

Crystal data, data collection and structure refinement details for **6c**, **6d** and **6e** are summarized in Table 1. H atoms

were placed in calculated positions and refined using a riding model, with C—H distances of 0.95 (aromatic) and 0.98 Å (CH_3), and $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}(C)$ for methyl groups.

2.3. *In vitro* cell tests

The synthesized compounds **6a–6i** were evaluated for their cytotoxicity against two human cancer cell lines, including KB (epidermoid carcinoma cancer) and HepG2 (hepatoma carcinoma cancer). The cell lines were obtained from the American Type Culture Collection (USA) ATCC. The cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum, 100 U ml^{-1} penicillin, and 100 µg ml^{-1} streptomycin at 310 K in a humidified atmosphere (95% air and 5% CO_2). The exponentially growing cells were used throughout the experiments. The inhibitory effects of the compounds on the growth of the human cancer cell lines were determined by measuring metabolic activity using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Briefly, human cancer cell lines (1 × 105 cells/ml) were treated for 3 d with a series of concentrations of the compounds (in DMSO), *i.e.* 0.125, 0.5, 2.0, 8.0, 32.0, and 128.0 µg ml^{-1}. After incubation, 0.1 mg MTT solution (50 µl of a 2 mg ml^{-1} solution) was added to each well and the cells were then incubated at 310 K for 4 h. The plates were centrifuged at 1000 rpm for 10 min at room temperature and the media were then carefully aspirated. DMSO (150 µl) was added to each well to dissolve the formazan crystals. The plates were read immediately at 540 nm on a microplate reader (TECAN GENIOUS). All the experiments were performed three times and the mean absorbance values were calculated. The results are expressed as the percentage of inhibition that produced a reduction in the absorbance by the treatment of the compounds compared to the untreated controls. A dose-response curve was generated and the inhibitory concentration of 50% (IC_{50}) was determined for each compound as well as for each cell line.

3. Results and discussion

3.1. Synthesis of 1,3,4-oxadiazoline derivatives 6a–6i

Nine new 2-(4-acetyl-5-aryl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-iodophenyl acetate derivatives, **6a–6i**, were synthesized starting from salicylic acid **1** (Scheme 1). In the initial steps, salicylic acid **1** is converted into 2-hydroxy-5-iodobenzohydrazide **4**. The IR spectrum of **4** shows an absorption at 1626 cm^{-1} corresponding to a C═O stretching vibration of the amide group. Two bands at 3405 and 3322 cm^{-1} are due to the presence of OH and NH_2 groups, respectively. The ^{1}H NMR spectrum of **4**, displays a broad singlet at 4.80 ppm (2H) corresponding to the NH_2 protons. Two broad peaks appear at δ 12.41 and 10.12 ppm, representing the OH and NHCO protons. The appearance of three signals in the aromatic area at 8.12 (1H, doublet, ^4J = 2.0 Hz), 7.6 (1H, doublet of doublet, ^3J = 9.0 Hz, ^4J = 2.0 Hz) and 6.75 ppm (1H, doublet, ^3J = 9.0 Hz) indicate that the benzene ring contains three substituents at positions of 1, 2 and 5.

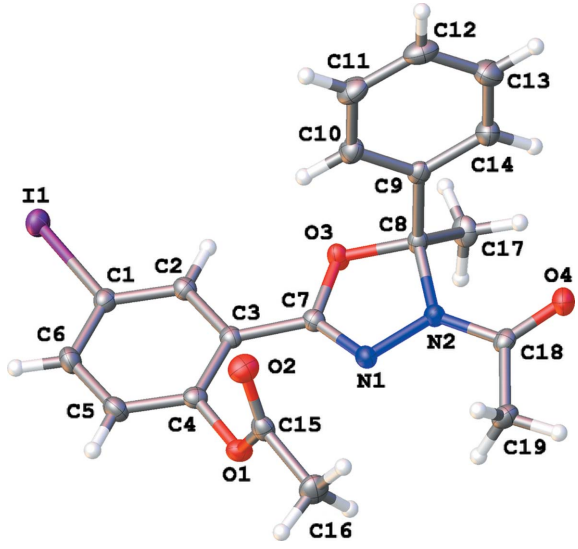


Figure 1
The molecular structure of **6c**, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

The reaction of aromatic ketones with hydrazide **4** to obtain the desired *N*-substituted hydrazides **5a–5i** occurs easily and may be observed clearly by the appearance of a precipitate during and after the progress of the reaction. In comparison with **4**, the corresponding *N*′-(1-arylethylidene)-2-hydroxy-5-iodobenzohydrazides **5a–5i** show similar spectra, except for the absence of bands due to the NH_2 group. Each compound shows absorptions at 1636–1645 and 1535–1605 cm^{-1} corresponding to C═O and C═N or C═C bonds present in the molecule. Besides that, the absorption around 2917–2940 cm^{-1} corresponds to the CH_3 group present in the *N*-substituted hydrazides.

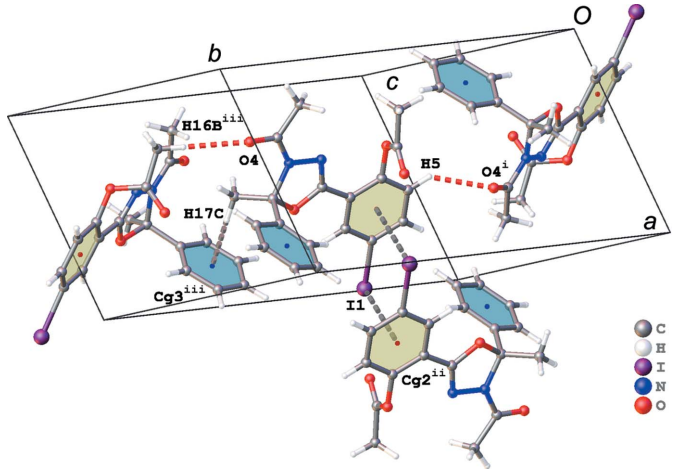


Figure 2
Packing diagram for **6c**, showing C—H···O (red), C—I···π (grey) and C—H···π (grey) interactions. *Cg*2 is the centroid of the C1–C6 ring and *Cg*3 is the centroid of the C9–C14 ring. [Symmetry codes: (i) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (ii) $-x+2, -y+1, -z+1$; (iii) $x, -y+\frac{3}{2}, z+\frac{1}{2}$.]

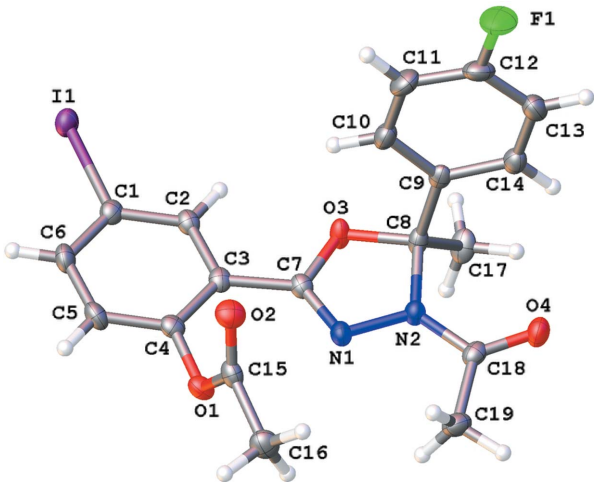


Figure 3
The molecular structure of **6d**, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

Hydrazones **5a**–**5i** on cyclization with acetic anhydride afforded 1,3,4-oxadiazoline derivatives **6a**–**6i**. In the IR spectra of 1,3,4-oxadiazoline compounds **6a**–**6h** (except for **6i**), no N—H bond stretching is present around 3200 cm^{-1}, while strong bands in the ranges 1751—1767 and 1651–1667 cm^{-1} indicated the presence of acetyl groups. Comparing the ^{13}C NMR spectra of **5a**–**5i** with those of **6a**–**6i** showed the appearance of a signal around 100.00 ppm; this was assigned to the C-5 atom of the oxadiazoline ring, *i.e.* atom C8. Besides that, the signals of the methyl group in the ^{1}H NMR spectra of **5a**–**5i** were shifted upfield in the ^{1}H NMR spectra of **6a**–**6i**. Those spectral characteristics are compatible with the transformation of hydrazones to oxadiazoline compounds.

Table 2
Hydrogen-bond geometry (Å, °) for **6c**.

*Cg*3 is the centroid of the C9–C14 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H5···O4^{i}	0.95	2.51	3.2828 (19)	139
C16—H16*B*···O4^{ii}	0.98	2.55	3.529 (2)	177
C17—H17*C*···*Cg*3^{iii}	0.98	2.70	3.5766 (17)	150

Symmetry codes: (i) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (ii) $x, -y+\frac{3}{2}, z-\frac{1}{2}$; (iii) $x, -y+\frac{3}{2}, z+\frac{1}{2}$.

3.2. Crystal structures of 1,3,4-oxadiazoline derivatives 6c, 6d and 6e

Crystallization experiments for compounds **6a**–**6i** using a mixture of ethanol and water resulted in crystals suitable for X-ray diffraction for compounds **6c**, **6d** and **6e**. The crystals belong to the monoclinic space group $P2_1/c$.

The central 1,3,4-oxadiazoline ring in **6c** displays an envelope conformation (Fig. 1) with the C8 atom as the flap [puckering parameters: $Q = 0.1310$ (14) Å and $\varphi = 322.2$ (6)°]. The best plane through the 1,3,4-oxadiazoline ring makes angles of 7.84 (8) and 78.48 (8)° with the 4-iodophenyl ring (atoms C1–C6) and the phenyl ring (atoms C9–C14), respectively. Both aromatic rings are inclined to each other by 82.11 (8)°.

In the crystal, molecules of **6c** are linked by C—H···O and C—H···π interactions, forming chains propagating along the *b*-axis direction (Fig. 2 and Table 2). Molecules in parallel chains form inversion dimers by I···π interactions [Fig. 2; I···*Cg*2^{iv} = 3.7888 (8) Å; *Cg*2 is the centroid of the C1–C6 ring; symmetry code: (iv) $-x+2, -y+1, -z+1$].

The crystal structures of **6c** and **6d** (Fig. 3) are isomorphous; the r.m.s. overlay fit is 0.0438 Å for the non-H atoms. The

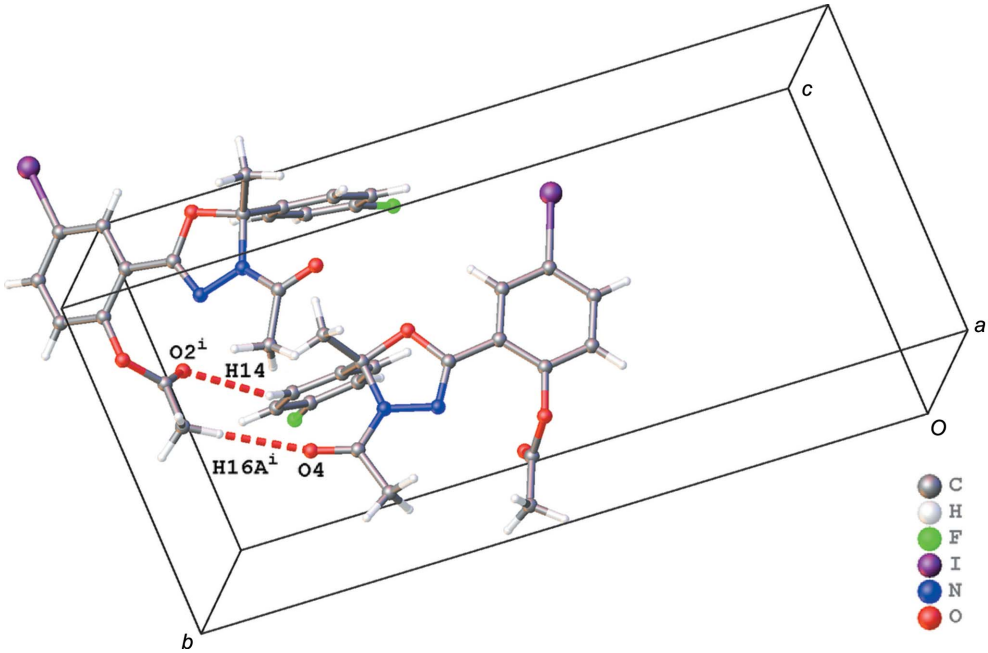


Figure 4
Partial packing diagram for **6d**, showing dimer formation by C—H···O (red) interactions. [Symmetry code: (i) $x, -y+\frac{3}{2}, z+\frac{1}{2}$.]

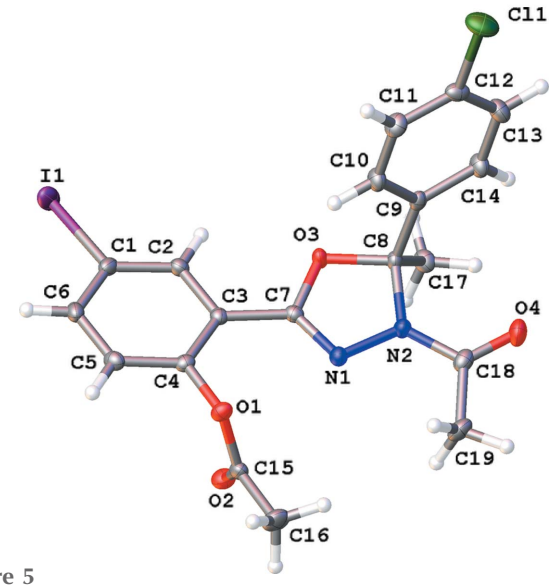


Figure 5
The molecular structure of **6e**, showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

puckering parameters of the 1,3,4-oxadiazoline ring of **6d** are Q = 0.1159 (17) Å and φ = 325.4 (8)°.

The crystal packing is built up by C—H···O, C—H···π and C—I···π interactions, as for **6c** [Table 3; I···*Cg*2^{i} = 3.7807 (8) Å; *Cg*2 is the centroid of the C1–C6 ring; symmetry code: (i) $-x+2, -y+1, -z+1$]. In addition, a C14—H14···O2^{ii} interaction (Table 3) is observed, which together

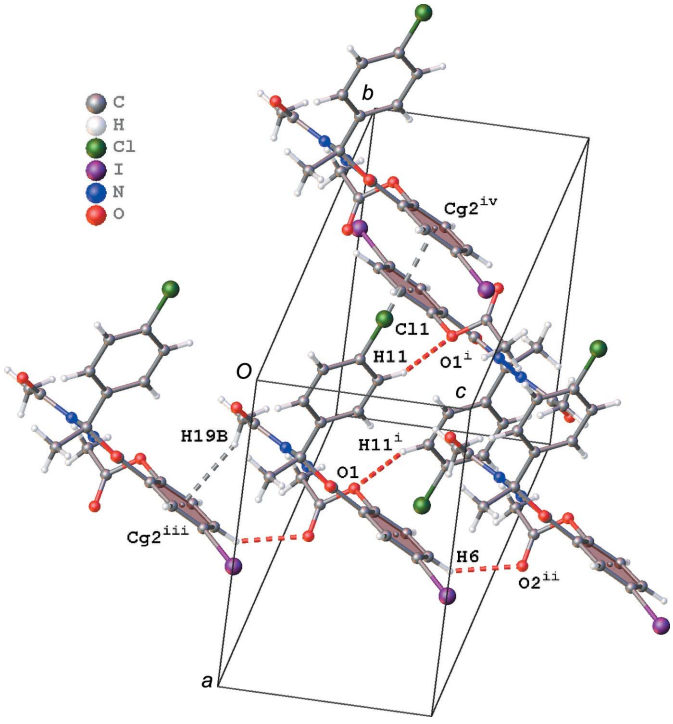


Figure 6
Partial packing diagram for **6e**, showing C—H···O (red), C—H···π (grey) and C—Cl···π (grey) interactions. *Cg*2 is the centroid of the C1–C6 ring. [Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $x, y, z+1$; (iii) $x, y, z-1$; (iv) $x-1, y, z$.]

Table 3
Hydrogen-bond geometry (Å, °) for **6d**.

*Cg*3 is the centroid of the C9–C14 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H5···O4^{i}	0.95	2.53	3.331 (2)	142
C14—H14···O2^{ii}	0.95	2.51	3.335 (2)	145
C16—H16*A*···O4^{iii}	0.98	2.54	3.513 (2)	174
C17—H17*C*···*Cg*3^{ii}	0.98	2.50	3.407 (2)	154

Symmetry codes: (i) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (ii) $x, -y+\frac{3}{2}, z+\frac{1}{2}$; (iii) $x, -y+\frac{3}{2}, z-\frac{1}{2}$.

Table 4
Hydrogen-bond geometry (Å, °) for **6e**.

*Cg*2 is the centroid of the C1–C6 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6···O2^{i}	0.95	2.47	3.258 (2)	140
C11—H11···O1^{ii}	0.95	2.55	3.435 (2)	155
C19—H19*B*···*Cg*2^{iii}	0.98	2.75	3.649 (2)	153

Symmetry codes: (i) $x, y, z+1$; (ii) $-x+1, -y+1, -z+1$; (iii) $x, y, z-1$.

with the C16—H16*A*···O4^{iii} interaction, results in the formation of a dimer, generating an $R_2^2(11)$ loop (Fig. 4).

Compound **6e** is not isomorphous with analogues **6c** and **6d**. The 1,3,4-oxadiazoline ring is almost planar (r.m.s. deviation = 0.024 Å) and is inclined to the planes of the aromatic rings by 11.95 (8) (ring C1–C6) and 78.28 (8)° (ring C9–C14) (Fig. 5). The orientation of the acetate group in **6e** is different compared to compounds **6c** and **6d**, as illustrated by the torsion angle C3—C4—O1—C15 [−83.55 (18)° in **6e**, 81.17 (17)° in **6c** and 81.5 (2)° in **6d**]. As a result, in structures **6c** and **6d**, the acetate group and the C8-aryl substituent are *syn* with respect to one another, while in **6e** they are *anti*. In all three cases, the carbonyl O atom (O4) of acetate is close to being eclipsed with respect to atom C4 of the aromatic ring, which may indicate a favourable interaction between a non-bonded pair of electrons on O4 and the π^* orbital of the aromatic C1–C6 ring.

In the crystal, inversion dimers are formed by C11—H11···O1^{ii} interactions (Table 4 and Fig. 6). These dimers interact further by C6—H6···O2^{i} and C19—H19*B*···π^{iii} interactions with the iodo-substituted phenyl ring (Table 4 and Fig. 6), resulting in chains of molecules running in the *c* direction. Parallel chains interact further by Cl···π contacts, again with the iodo-substituted phenyl ring (Table 4 and Fig. 6). In contrast to the crystal packings of the two previous analogues, the packing of **6e** does not show I···π interactions. The closest neighbour for atom I1 is H17*B* (I1···H17*B*^{i} = 3.13 Å). The shortest I···Cl distance in the crystal packing is I1···Cl1^{iv} = 3.850 (2) Å [symmetry code: (iv) $x+1, -y+\frac{1}{2}, z+\frac{1}{2}$].

The crystal packings of compounds **6c**, **6d** and **6e** contain no voids.

3.3. *In vitro* cytotoxicity of compounds 6a–6i

Complexes **6a–6i** were assayed for *in vitro* cytotoxicity against human cancer cells KB-CCL-17 (Human epidemic

carcinoma) and Hep-G2-HB-8065 (Hepatocellular carcinoma). The IC_{50} values are listed in Table 5, together with literature data for ellipcitine (Hoang *et al.*, 2015).

The results indicate that most of the examined compounds possess at least moderate cytotoxic activity, and some compounds even display a promising activity profile. It is important to note that these separate pharmacophores display considerably less potent cytotoxic activities (IC_{50} values ranging from 42 to more than 400 μM) compared to the most promising compounds **6d**, **6e**, **6f** and **6h** (IC_{50} values between 0.9 and 4.5 μM), showing a reasonable activity against two human cancer cell lines. In particular, compound **6f** exhibits a strong anticancer effect against KB cells, with an IC_{50} value (0.9 μM) lower than ellipticine (1.2 μM).

Table 5
Cytotoxic effects of the examined compounds **6a**–**6i** (IC_{50}[a] in μM).

Compound	KB	Hep-G2
6a	**3.733**±0.472	12.574±0.766
6b	9.214±0.884	14.735±0.727
6c	5.280±0.819	12.284±0.625
6d	**1.867**±0.568	**4.564**±0.539
6e	**4.012**±0.622	**3.811**±0.822
6f	**0.921**±0.360	**3.315**±0.552
6g	6.262±0.645	13.260±0.866
6h	**3.166**±0.398	**3.983**±0.482
6i	12.476±0.979	11.900±1.036
Ellipcitine	1.260±0,528	2.358±0.407

Note: (*a*) IC_{50} is the concentration of the compound required to inhibit cell growth by 50%.

4. Conclusions

In this study, we have synthesized nine new 2-(4-acetyl-5-aryl-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-iodophenyl acetate compounds in five steps starting from salicylic acid with moderate yield. The compounds were characterized spectroscopically and by single-crystal X-ray diffraction for **6c**, **6d** and **6e**. The *in vitro* cytotoxicity of **6a**–**6i** against two human cancer cell lines (KB and Hep-G2) was determined and illustrated, implying their potential for further studies in the field of anticancer research.

References

Bruker (2013). *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.

Bruker (2014). *APEX2* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

Cong, N. T., Tung, N. Q., Minh Nguyen, N. T. & Chi, N. T. (2012). *Viet. J. Chem.* **50**, 12–15.

Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). *J. Appl. Cryst.* **42**, 339–341.

El Sadek, M. M., Hassan, S. Y., Abdelwahab, H. E. & Yacout, G. A. (2013). *Molecules*, **18**, 8550–8562.

Fadda, A. A., Abdel-Rahman, A. A.-H., El-Sayed, W. A., Zidan, T. A. & Badria, F. A. (2011). *Chem. Heterocycl. Compd*, **47**, 856–864.

Hamdi, N., Passarelli, V. & Romerosa, A. (2011). *C. R. Chim.* **14**, 548–555.

Hoang, L. T. A., Nguyen, T. C., Bui, H. T., Pham, H. Y., Nguyen, X. N., Do, T. T., Nguyen, H. N., Chau, V. M., Phan, V. K. & Young, H. K. (2015). *Molecules*, **20**, 1151–1160.

Huang, G., Cheng, H., Liu, Y. & Hu, J. (2018). *Saudi Pharm. J.* **26**, 263–265.

Joshi, S. D., Vagdevi, H. M., Vaidya, V. P. & Gadaginamath, G. S. (2008). *Eur. J. Med. Chem.* **43**, 1989–1996.

Kantouch, A., El-Sayed, A. A., Salama, M., El-Kheir, A. A. & Mowafi, S. (2013). *Int. J. Biol. Macromol.* **62**, 603–607.

Ke, S., Liu, F., Wang, N., Yang, Q. & Qian, X. (2009). *Bioorg. Med. Chem. Lett.* **19**, 332–335.

Khiati, Z., Othman, A. A. & Guessas, B. (2007). *S. Afr. J. Chem.* **60**, 20–24.

Kotb, E. R., El-Hashash, M. A., Salama, M. A., Kalf, H. S. & Abdel Wahed, N. A. M. (2009). *Acta Chim. Slov.* **56**, 908–919.

Manojkumar, P., Ravi, T. K. & Subbuchettiar, G. (2009). *Acta Pharm.* **59**, 159–170.

Mohitea, P. B. & Bhaskar, V. H. (2011). *Orbital: Electron. J. Chem.* **3**, 117–124.

Murty, M. S. R., Penthala, R., Nath, L. R. & Anto, R. J. (2014). *Lett. Drug. Des. Discov.* **11**, 1133–1142.

Naveena, C. S., Poojary, B., Kumsi, M., Thangavel, A. & Shenoy, S. (2011). *Der Pharma Chem.* **3**, 247–257.

Pattan, S. R., Rabara, P. A., Pattan, J. S., Bukitagar, A. A., Wakale, V. S. & Musmade, D. S. (2009). *Indian J. Chem. Sect. B*, **48**, 1453–1456.

Rajak, H., Kharya, M. D. & Mishra, P. (2007). *Yakugaku Zasshi*, **127**, 1757–1764.

Sahoo, U., Seth, A. K. & Balaraman, R. (2014). *Int. J. ChemTech Res.* **6**, 2427–2437.

Sarshira, E. M., Hamada, N. M., Moghazi, Y. M. & Abdelrahman, M. M. (2016). *J. Heterocycl. Chem.* **53**, 1970–1982.

Sheldrick, G. M. (2008). *Acta Cryst.* A**64**, 112–122.

Sheldrick, G. M. (2015*a*). *Acta Cryst.* A**71**, 3–8.

Sheldrick, G. M. (2015*b*). *Acta Cryst.* C**71**, 3–8.

Suresh Kumar, G. V., Rajendraprasad, Y., Mallikarjuna, B. P., Chandrashekar, S. M. & Kistayya, C. (2010). *Eur. J. Med. Chem.* **45**, 2063–2074.

Vejselova, D. & Kutlu, H. M. (2015). *Turk. J. Biol.* **39**, 1–5.

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Synthesis, structure and *in vitro* cytotoxicity testing of some 1,3,4-oxadiazoline derivatives from 2-hydroxy-5-iodobenzoic acid

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Computing details

For all structures, data collection: *APEX2* (Bruker, 2014); cell refinement: *SAINT* (Bruker, 2013); data reduction: *SAINT* (Bruker, 2013). Program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008) for (6c), (6e); SHELXT (Sheldrick, 2015a) for (6d). For all structures, program(s) used to refine structure: *SHELXL2014* (Sheldrick, 2015b); molecular graphics: OLEX2 (Dolomanov *et al.*, 2009); software used to prepare material for publication: OLEX2 (Dolomanov *et al.*, 2009).

2-(4-Acetyl-5-methyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-iodophenyl acetate (6c)

Crystal data

$C_{19}H_{17}IN_2O_4$
M_r = 464.24
Monoclinic, $P2_1/c$
a = 8.837 (1) Å
b = 20.056 (1) Å
c = 11.015 (1) Å
β = 110.18 (1)°
V = 1832.4 (3) Å^3
Z = 4
$F(000)$ = 920
D_x = 1.683 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 9773 reflections
θ = 3.2–33.1°
μ = 1.77 mm^{-1}
T = 100 K
Block, colourless
0.42 × 0.20 × 0.16 mm

Data collection

Bruker APEXII CCD diffractometer
φ and ω scans
Absorption correction: multi-scan (SADABS; Bruker, 2014)
T_{min} = 0.627, T_{max} = 0.747
54289 measured reflections
5600 independent reflections
4994 reflections with $I > 2\sigma(I)$
R_{int} = 0.029
θ_{max} = 30.5°, θ_{min} = 2.8°
h = −12→12
k = −28→28
l = −15→15

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.022
$wR(F^2)$ = 0.050
S = 1.05
5600 reflections
238 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0212P)^2 + 1.2207P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003

$\Delta\rho_{max}$ = 0.97 e Å^{-3} $\Delta\rho_{min}$ = −0.59 e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
I1	1.02273 (2)	0.44378 (2)	0.71043 (2)	0.02391 (4)
O1	0.42189 (12)	0.51004 (5)	0.22300 (10)	0.0198 (2)
N1	0.44105 (14)	0.63918 (6)	0.32433 (11)	0.0172 (2)
C1	0.81918 (17)	0.46520 (7)	0.54844 (14)	0.0185 (3)
O2	0.57214 (14)	0.56173 (6)	0.12194 (11)	0.0265 (2)
N2	0.43632 (14)	0.70564 (6)	0.36222 (11)	0.0170 (2)
C2	0.75217 (17)	0.52839 (7)	0.53642 (13)	0.0177 (3)
H2	0.795397	0.560319	0.603141	0.021*
O3	0.63889 (13)	0.65492 (5)	0.51584 (9)	0.0191 (2)
C3	0.62097 (16)	0.54536 (7)	0.42630 (13)	0.0162 (2)
O4	0.31986 (13)	0.80687 (5)	0.32597 (11)	0.0240 (2)
C4	0.55900 (17)	0.49706 (7)	0.33034 (13)	0.0175 (3)
C5	0.62622 (19)	0.43404 (7)	0.34230 (15)	0.0221 (3)
H5	0.582960	0.401921	0.275960	0.027*
C6	0.75733 (19)	0.41777 (7)	0.45167 (15)	0.0226 (3)
H6	0.804238	0.374628	0.460211	0.027*
C7	0.55901 (16)	0.61343 (7)	0.41634 (13)	0.0161 (2)
C8	0.58015 (17)	0.72191 (7)	0.47773 (13)	0.0165 (2)
C9	0.70562 (16)	0.76014 (7)	0.43953 (13)	0.0170 (2)
C10	0.82350 (18)	0.72550 (8)	0.40745 (15)	0.0225 (3)
H10	0.828901	0.678281	0.414448	0.027*
C11	0.93294 (19)	0.75959 (9)	0.36537 (16)	0.0289 (3)
H11	1.012829	0.735524	0.343917	0.035*
C12	0.92662 (19)	0.82828 (9)	0.35443 (16)	0.0294 (3)
H12	1.001008	0.851359	0.324678	0.035*
C13	0.8109 (2)	0.86321 (9)	0.38721 (17)	0.0299 (3)
H13	0.806516	0.910437	0.380223	0.036*
C14	0.70118 (18)	0.82959 (8)	0.43030 (15)	0.0235 (3)
H14	0.623057	0.853966	0.453485	0.028*
C15	0.44235 (18)	0.54575 (7)	0.12345 (14)	0.0197 (3)
C16	0.2830 (2)	0.55892 (8)	0.02103 (15)	0.0274 (3)
H16A	0.245772	0.518532	−0.030777	0.041*
H16B	0.294126	0.595176	−0.034930	0.041*
H16C	0.204476	0.571687	0.061592	0.041*
C17	0.5379 (2)	0.75217 (8)	0.58752 (14)	0.0236 (3)
H17A	0.456948	0.724354	0.605601	0.035*
H17B	0.494300	0.797093	0.563247	0.035*
H17C	0.634896	0.754692	0.664922	0.035*

C18	0.31788 (16)	0.74827 (7)	0.29343 (13)	0.0176 (3)
C19	0.18862 (18)	0.71930 (8)	0.17778 (15)	0.0227 (3)
H19A	0.101667	0.751907	0.143604	0.034*
H19B	0.145536	0.678758	0.203469	0.034*
H19C	0.234431	0.708341	0.110914	0.034*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
I1	0.02366 (5)	0.02116 (5)	0.02296 (5)	0.00370 (3)	0.00299 (4)	0.00274 (3)
O1	0.0188 (5)	0.0201 (5)	0.0183 (5)	−0.0032 (4)	0.0038 (4)	0.0003 (4)
N1	0.0175 (5)	0.0151 (5)	0.0192 (5)	0.0000 (4)	0.0065 (4)	−0.0022 (4)
C1	0.0184 (6)	0.0178 (6)	0.0192 (6)	0.0005 (5)	0.0064 (5)	0.0028 (5)
O2	0.0257 (6)	0.0309 (6)	0.0238 (5)	−0.0008 (4)	0.0096 (4)	0.0042 (4)
N2	0.0163 (5)	0.0159 (5)	0.0175 (5)	0.0010 (4)	0.0041 (4)	−0.0023 (4)
C2	0.0192 (6)	0.0171 (6)	0.0173 (6)	−0.0010 (5)	0.0070 (5)	0.0001 (5)
O3	0.0241 (5)	0.0154 (5)	0.0148 (4)	0.0027 (4)	0.0029 (4)	−0.0007 (4)
C3	0.0167 (6)	0.0158 (6)	0.0175 (6)	−0.0008 (5)	0.0078 (5)	0.0003 (5)
O4	0.0233 (5)	0.0190 (5)	0.0290 (5)	0.0038 (4)	0.0083 (4)	0.0007 (4)
C4	0.0173 (6)	0.0180 (6)	0.0172 (6)	−0.0026 (5)	0.0060 (5)	0.0009 (5)
C5	0.0257 (7)	0.0166 (7)	0.0230 (7)	−0.0025 (5)	0.0070 (6)	−0.0029 (5)
C6	0.0263 (7)	0.0145 (6)	0.0264 (7)	0.0014 (5)	0.0082 (6)	0.0002 (5)
C7	0.0177 (6)	0.0165 (6)	0.0151 (6)	−0.0008 (5)	0.0068 (5)	−0.0013 (5)
C8	0.0182 (6)	0.0165 (6)	0.0141 (6)	0.0028 (5)	0.0046 (5)	−0.0010 (5)
C9	0.0162 (6)	0.0197 (6)	0.0133 (6)	0.0008 (5)	0.0028 (5)	−0.0022 (5)
C10	0.0198 (7)	0.0243 (7)	0.0235 (7)	0.0021 (5)	0.0077 (5)	−0.0033 (6)
C11	0.0195 (7)	0.0388 (9)	0.0304 (8)	0.0001 (6)	0.0111 (6)	−0.0033 (7)
C12	0.0201 (7)	0.0400 (9)	0.0272 (8)	−0.0065 (6)	0.0071 (6)	0.0020 (7)
C13	0.0276 (8)	0.0243 (8)	0.0361 (9)	−0.0043 (6)	0.0090 (7)	0.0014 (7)
C14	0.0214 (7)	0.0208 (7)	0.0279 (7)	0.0015 (5)	0.0080 (6)	−0.0018 (6)
C15	0.0245 (7)	0.0168 (6)	0.0169 (6)	0.0003 (5)	0.0058 (5)	−0.0021 (5)
C16	0.0264 (8)	0.0299 (8)	0.0206 (7)	0.0022 (6)	0.0014 (6)	−0.0003 (6)
C17	0.0307 (8)	0.0251 (7)	0.0179 (6)	0.0042 (6)	0.0122 (6)	−0.0020 (5)
C18	0.0149 (6)	0.0204 (6)	0.0195 (6)	0.0017 (5)	0.0085 (5)	0.0026 (5)
C19	0.0162 (6)	0.0265 (7)	0.0231 (7)	0.0008 (5)	0.0040 (5)	0.0013 (6)

Geometric parameters (Å, º)

I1—C1	2.0951 (14)	C9—C10	1.395 (2)
O1—C4	1.3948 (17)	C9—C14	1.396 (2)
O1—C15	1.3727 (17)	C10—H10	0.9500
N1—N2	1.4017 (16)	C10—C11	1.388 (2)
N1—C7	1.2851 (18)	C11—H11	0.9500
C1—C2	1.386 (2)	C11—C12	1.382 (3)
C1—C6	1.392 (2)	C12—H12	0.9500
O2—C15	1.1966 (19)	C12—C13	1.386 (2)
N2—C8	1.4917 (18)	C13—H13	0.9500
N2—C18	1.3614 (18)	C13—C14	1.392 (2)

C2—H2	0.9500	C14—H14	0.9500
C2—C3	1.4004 (19)	C15—C16	1.493 (2)
O3—C7	1.3631 (16)	C16—H16A	0.9800
O3—C8	1.4493 (16)	C16—H16B	0.9800
C3—C4	1.3986 (19)	C16—H16C	0.9800
C3—C7	1.4610 (19)	C17—H17A	0.9800
O4—C18	1.2270 (18)	C17—H17B	0.9800
C4—C5	1.383 (2)	C17—H17C	0.9800
C5—H5	0.9500	C18—C19	1.504 (2)
C5—C6	1.392 (2)	C19—H19A	0.9800
C6—H6	0.9500	C19—H19B	0.9800
C8—C9	1.522 (2)	C19—H19C	0.9800
C8—C17	1.5107 (19)		

C15—O1—C4	117.34 (11)	C11—C10—H10	119.8
C7—N1—N2	104.29 (11)	C10—C11—H11	119.7
C2—C1—I1	118.81 (10)	C12—C11—C10	120.55 (15)
C2—C1—C6	120.65 (13)	C12—C11—H11	119.7
C6—C1—I1	120.47 (11)	C11—C12—H12	120.3
N1—N2—C8	110.97 (11)	C11—C12—C13	119.49 (15)
C18—N2—N1	121.85 (12)	C13—C12—H12	120.3
C18—N2—C8	127.06 (12)	C12—C13—H13	119.8
C1—C2—H2	119.9	C12—C13—C14	120.47 (16)
C1—C2—C3	120.26 (13)	C14—C13—H13	119.8
C3—C2—H2	119.9	C9—C14—H14	119.9
C7—O3—C8	107.38 (10)	C13—C14—C9	120.17 (15)
C2—C3—C7	117.97 (12)	C13—C14—H14	119.9
C4—C3—C2	118.53 (13)	O1—C15—C16	110.24 (13)
C4—C3—C7	123.48 (13)	O2—C15—O1	122.81 (13)
O1—C4—C3	120.69 (12)	O2—C15—C16	126.93 (14)
C5—C4—O1	118.05 (12)	C15—C16—H16A	109.5
C5—C4—C3	121.16 (13)	C15—C16—H16B	109.5
C4—C5—H5	120.0	C15—C16—H16C	109.5
C4—C5—C6	119.91 (14)	H16A—C16—H16B	109.5
C6—C5—H5	120.0	H16A—C16—H16C	109.5
C1—C6—H6	120.3	H16B—C16—H16C	109.5
C5—C6—C1	119.49 (14)	C8—C17—H17A	109.5
C5—C6—H6	120.3	C8—C17—H17B	109.5
N1—C7—O3	116.29 (12)	C8—C17—H17C	109.5
N1—C7—C3	128.01 (13)	H17A—C17—H17B	109.5
O3—C7—C3	115.68 (12)	H17A—C17—H17C	109.5
N2—C8—C9	111.22 (11)	H17B—C17—H17C	109.5
N2—C8—C17	113.42 (12)	N2—C18—C19	116.25 (13)
O3—C8—N2	99.15 (10)	O4—C18—N2	120.54 (13)
O3—C8—C9	108.96 (11)	O4—C18—C19	123.21 (13)
O3—C8—C17	107.66 (11)	C18—C19—H19A	109.5
C17—C8—C9	115.08 (12)	C18—C19—H19B	109.5
C10—C9—C8	119.86 (13)	C18—C19—H19C	109.5

C10—C9—C14	118.89 (14)	H19A—C19—H19B	109.5
C14—C9—C8	121.19 (13)	H19A—C19—H19C	109.5
C9—C10—H10	119.8	H19B—C19—H19C	109.5
C11—C10—C9	120.41 (15)		

I1—C1—C2—C3	176.86 (10)	C6—C1—C2—C3	0.0 (2)
I1—C1—C6—C5	−177.27 (11)	C7—N1—N2—C8	9.02 (14)
O1—C4—C5—C6	−176.23 (13)	C7—N1—N2—C18	−174.80 (12)
N1—N2—C8—O3	−13.43 (13)	C7—O3—C8—N2	12.66 (13)
N1—N2—C8—C9	101.12 (13)	C7—O3—C8—C9	−103.64 (12)
N1—N2—C8—C17	−127.29 (12)	C7—O3—C8—C17	130.93 (12)
N1—N2—C18—O4	−177.27 (12)	C7—C3—C4—O1	−6.1 (2)
N1—N2—C18—C19	2.50 (19)	C7—C3—C4—C5	177.43 (13)
C1—C2—C3—C4	0.6 (2)	C8—N2—C18—O4	−1.7 (2)
C1—C2—C3—C7	−177.68 (13)	C8—N2—C18—C19	178.03 (12)
N2—N1—C7—O3	−0.09 (16)	C8—O3—C7—N1	−8.94 (16)
N2—N1—C7—C3	−178.50 (13)	C8—O3—C7—C3	169.68 (11)
N2—C8—C9—C10	−88.99 (15)	C8—C9—C10—C11	176.32 (14)
N2—C8—C9—C14	88.16 (15)	C8—C9—C14—C13	−175.89 (14)
C2—C1—C6—C5	−0.4 (2)	C9—C10—C11—C12	−0.1 (2)
C2—C3—C4—O1	175.70 (12)	C10—C9—C14—C13	1.3 (2)
C2—C3—C4—C5	−0.8 (2)	C10—C11—C12—C13	0.7 (3)
C2—C3—C7—N1	179.85 (14)	C11—C12—C13—C14	−0.3 (3)
C2—C3—C7—O3	1.42 (18)	C12—C13—C14—C9	−0.7 (3)
O3—C8—C9—C10	19.29 (17)	C14—C9—C10—C11	−0.9 (2)
O3—C8—C9—C14	−163.56 (12)	C15—O1—C4—C3	81.18 (16)
C3—C4—C5—C6	0.3 (2)	C15—O1—C4—C5	−102.23 (15)
C4—O1—C15—O2	5.2 (2)	C17—C8—C9—C10	140.28 (14)
C4—O1—C15—C16	−176.26 (12)	C17—C8—C9—C14	−42.57 (18)
C4—C3—C7—N1	1.6 (2)	C18—N2—C8—O3	170.64 (12)
C4—C3—C7—O3	−176.80 (12)	C18—N2—C8—C9	−74.81 (16)
C4—C5—C6—C1	0.3 (2)	C18—N2—C8—C17	56.77 (18)

Hydrogen-bond geometry (Å, º)

*Cg*3 is the centroid of the C9–C14 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H5···O4^{i}	0.95	2.51	3.2828 (19)	139
C16—H16*B*···O4^{ii}	0.98	2.55	3.529 (2)	177
C17—H17*C*···*Cg*3^{iii}	0.98	2.70	3.5766 (17)	150

Symmetry codes: (i) −*x*+1, *y*−1/2, −*z*+1/2; (ii) *x*, −*y*+3/2, *z*−1/2; (iii) *x*, −*y*+3/2, *z*+1/2.

2-[4-Acetyl-5-(4-fluorophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (6d)

Crystal data

$C_{19}H_{16}FIN_2O_4$	*a* = 9.1241 (4) Å
M_r = 482.24	*b* = 20.0980 (9) Å
Monoclinic, $P2_1/c$	*c* = 10.7456 (5) Å

β = 110.224 (2)°
V = 1849.00 (15) Å^3
Z = 4
F(000) = 952
D_x = 1.732 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å

Cell parameters from 9994 reflections
θ = 2.9–30.5°
μ = 1.77 mm^{-1}
T = 100 K
Block, colourless
0.60 × 0.37 × 0.29 mm

Data collection

Bruker APEXII CCD diffractometer
φ and ω scans
Absorption correction: multi-scan (SADABS; Bruker, 2014)
T_{min} = 0.610, T_{max} = 0.746
52242 measured reflections

4033 independent reflections
3703 reflections with $I > 2\sigma(I)$
R_{int} = 0.048
θ_{max} = 27.0°, θ_{min} = 2.7°
h = −11→11
k = −25→25
l = −13→13

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.020
$wR(F^2)$ = 0.047
S = 1.06
4033 reflections
247 parameters
0 restraints
Primary atom site location: iterative

Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0179P)^2 + 1.3214P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.56 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
I1	1.02927 (2)	0.43863 (2)	0.70991 (2)	0.02562 (5)
F1	0.99431 (14)	0.86573 (7)	0.31186 (15)	0.0482 (4)
O1	0.43234 (14)	0.50760 (6)	0.22482 (12)	0.0221 (3)
N1	0.45186 (17)	0.63451 (7)	0.33434 (14)	0.0196 (3)
C1	0.8281 (2)	0.46130 (9)	0.54780 (17)	0.0208 (3)
O2	0.56974 (16)	0.56291 (6)	0.11907 (14)	0.0287 (3)
N2	0.44708 (17)	0.70043 (7)	0.37438 (14)	0.0193 (3)
C2	0.7610 (2)	0.52365 (8)	0.54173 (17)	0.0193 (3)
H2	0.803774	0.554529	0.611907	0.023*
O3	0.64636 (15)	0.64956 (6)	0.52903 (12)	0.0221 (3)
C3	0.6303 (2)	0.54116 (8)	0.43227 (17)	0.0185 (3)
O4	0.33470 (15)	0.80138 (6)	0.34228 (13)	0.0275 (3)
C4	0.5691 (2)	0.49418 (8)	0.33133 (17)	0.0197 (3)
C5	0.6368 (2)	0.43237 (8)	0.33789 (19)	0.0244 (4)
H5	0.594019	0.401213	0.268247	0.029*
C6	0.7674 (2)	0.41554 (9)	0.44590 (19)	0.0247 (4)

H6	0.814835	0.373124	0.450193	0.030*
C7	0.5681 (2)	0.60868 (8)	0.42603 (16)	0.0185 (3)
C8	0.5860 (2)	0.71636 (8)	0.49331 (17)	0.0197 (3)
C9	0.7052 (2)	0.75722 (8)	0.45591 (16)	0.0190 (3)
C10	0.8228 (2)	0.72585 (9)	0.42326 (19)	0.0254 (4)
H10	0.835259	0.678999	0.433228	0.030*
C11	0.9221 (2)	0.76212 (10)	0.3763 (2)	0.0327 (4)
H11	1.002324	0.740675	0.353709	0.039*
C12	0.9018 (2)	0.82967 (10)	0.3632 (2)	0.0301 (4)
C13	0.7907 (2)	0.86302 (9)	0.3985 (2)	0.0293 (4)
H13	0.781470	0.910050	0.390699	0.035*
C14	0.6923 (2)	0.82630 (9)	0.44565 (18)	0.0242 (4)
H14	0.615284	0.848465	0.471304	0.029*
C15	0.4463 (2)	0.54563 (9)	0.12336 (18)	0.0221 (4)
C16	0.2891 (2)	0.55914 (10)	0.02252 (19)	0.0298 (4)
H16A	0.294383	0.599001	−0.028300	0.045*
H16B	0.213370	0.566258	0.067348	0.045*
H16C	0.256482	0.521035	−0.037665	0.045*
C17	0.5423 (2)	0.74413 (10)	0.60655 (18)	0.0274 (4)
H17A	0.463240	0.715531	0.621914	0.041*
H17B	0.500112	0.789140	0.584128	0.041*
H17C	0.635236	0.745718	0.686984	0.041*
C18	0.3312 (2)	0.74345 (9)	0.30679 (17)	0.0207 (3)
C19	0.2035 (2)	0.71544 (10)	0.1893 (2)	0.0281 (4)
H19A	0.119864	0.748393	0.156118	0.042*
H19B	0.161775	0.675041	0.215776	0.042*
H19C	0.245578	0.704600	0.119275	0.042*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
I1	0.02788 (7)	0.02021 (7)	0.02625 (7)	0.00422 (5)	0.00614 (5)	0.00214 (5)
F1	0.0294 (6)	0.0459 (8)	0.0738 (10)	−0.0073 (6)	0.0236 (7)	0.0089 (7)
O1	0.0241 (6)	0.0200 (6)	0.0208 (6)	−0.0051 (5)	0.0061 (5)	0.0002 (5)
N1	0.0225 (7)	0.0160 (7)	0.0217 (7)	0.0003 (5)	0.0094 (6)	−0.0008 (6)
C1	0.0221 (8)	0.0187 (8)	0.0227 (9)	0.0002 (7)	0.0091 (7)	0.0035 (7)
O2	0.0305 (7)	0.0300 (7)	0.0275 (7)	−0.0029 (6)	0.0125 (6)	0.0043 (6)
N2	0.0216 (7)	0.0172 (7)	0.0184 (7)	0.0024 (5)	0.0062 (6)	−0.0010 (6)
C2	0.0240 (9)	0.0172 (8)	0.0194 (8)	−0.0015 (6)	0.0109 (7)	−0.0002 (6)
O3	0.0313 (7)	0.0163 (6)	0.0156 (6)	0.0061 (5)	0.0043 (5)	−0.0008 (5)
C3	0.0224 (8)	0.0170 (8)	0.0197 (8)	−0.0004 (6)	0.0118 (7)	0.0020 (6)
O4	0.0282 (7)	0.0218 (7)	0.0317 (7)	0.0070 (5)	0.0092 (6)	0.0012 (5)
C4	0.0215 (8)	0.0190 (8)	0.0199 (8)	−0.0036 (6)	0.0087 (7)	0.0016 (7)
C5	0.0319 (10)	0.0163 (8)	0.0257 (9)	−0.0052 (7)	0.0106 (8)	−0.0036 (7)
C6	0.0313 (10)	0.0138 (8)	0.0308 (10)	0.0010 (7)	0.0131 (8)	0.0006 (7)
C7	0.0226 (8)	0.0180 (8)	0.0172 (8)	−0.0013 (6)	0.0098 (7)	−0.0008 (6)
C8	0.0248 (9)	0.0175 (8)	0.0152 (8)	0.0065 (7)	0.0050 (7)	0.0004 (6)
C9	0.0197 (8)	0.0201 (8)	0.0135 (8)	0.0027 (6)	0.0009 (6)	−0.0036 (6)

C10	0.0225 (9)	0.0230 (9)	0.0281 (10)	0.0061 (7)	0.0056 (7)	−0.0018 (7)
C11	0.0209 (9)	0.0361 (11)	0.0420 (12)	0.0058 (8)	0.0118 (9)	−0.0014 (9)
C12	0.0173 (9)	0.0344 (10)	0.0357 (11)	−0.0063 (8)	0.0056 (8)	0.0015 (9)
C13	0.0273 (10)	0.0207 (9)	0.0348 (11)	−0.0020 (7)	0.0044 (8)	−0.0012 (8)
C14	0.0233 (9)	0.0223 (9)	0.0243 (9)	0.0030 (7)	0.0048 (7)	−0.0044 (7)
C15	0.0305 (10)	0.0163 (8)	0.0203 (8)	−0.0011 (7)	0.0098 (7)	−0.0024 (7)
C16	0.0310 (10)	0.0299 (10)	0.0239 (9)	−0.0013 (8)	0.0037 (8)	0.0001 (8)
C17	0.0402 (11)	0.0280 (10)	0.0172 (9)	0.0084 (8)	0.0139 (8)	−0.0006 (7)
C18	0.0190 (8)	0.0228 (9)	0.0229 (9)	0.0032 (7)	0.0107 (7)	0.0045 (7)
C19	0.0189 (9)	0.0312 (10)	0.0318 (10)	0.0006 (7)	0.0055 (8)	0.0035 (8)

Geometric parameters (Å, º)

I1—C1	2.0979 (18)	C8—C17	1.512 (2)
F1—C12	1.365 (2)	C9—C10	1.390 (2)
O1—C4	1.397 (2)	C9—C14	1.395 (2)
O1—C15	1.373 (2)	C10—H10	0.9500
N1—N2	1.3983 (19)	C10—C11	1.387 (3)
N1—C7	1.281 (2)	C11—H11	0.9500
C1—C2	1.386 (2)	C11—C12	1.371 (3)
C1—C6	1.390 (3)	C12—C13	1.373 (3)
O2—C15	1.195 (2)	C13—H13	0.9500
N2—C8	1.491 (2)	C13—C14	1.386 (3)
N2—C18	1.364 (2)	C14—H14	0.9500
C2—H2	0.9500	C15—C16	1.493 (3)
C2—C3	1.400 (2)	C16—H16A	0.9800
O3—C7	1.365 (2)	C16—H16B	0.9800
O3—C8	1.4515 (19)	C16—H16C	0.9800
C3—C4	1.400 (2)	C17—H17A	0.9800
C3—C7	1.464 (2)	C17—H17B	0.9800
O4—C18	1.222 (2)	C17—H17C	0.9800
C4—C5	1.379 (2)	C18—C19	1.500 (3)
C5—H5	0.9500	C19—H19A	0.9800
C5—C6	1.387 (3)	C19—H19B	0.9800
C6—H6	0.9500	C19—H19C	0.9800
C8—C9	1.523 (2)		

C15—O1—C4	117.16 (13)	C11—C10—H10	119.6
C7—N1—N2	104.65 (14)	C10—C11—H11	120.8
C2—C1—I1	118.74 (13)	C12—C11—C10	118.38 (18)
C2—C1—C6	120.79 (17)	C12—C11—H11	120.8
C6—C1—I1	120.42 (13)	F1—C12—C11	119.10 (18)
N1—N2—C8	111.07 (13)	F1—C12—C13	118.09 (18)
C18—N2—N1	122.51 (14)	C11—C12—C13	122.81 (19)
C18—N2—C8	126.37 (14)	C12—C13—H13	120.9
C1—C2—H2	120.0	C12—C13—C14	118.30 (18)
C1—C2—C3	120.05 (16)	C14—C13—H13	120.9
C3—C2—H2	120.0	C9—C14—H14	119.6

C7—O3—C8	107.33 (12)	C13—C14—C9	120.78 (17)
C2—C3—C4	118.51 (16)	C13—C14—H14	119.6
C2—C3—C7	118.41 (15)	O1—C15—C16	110.38 (15)
C4—C3—C7	123.02 (16)	O2—C15—O1	122.66 (17)
O1—C4—C3	120.58 (15)	O2—C15—C16	126.93 (17)
C5—C4—O1	118.26 (15)	C15—C16—H16A	109.5
C5—C4—C3	121.07 (16)	C15—C16—H16B	109.5
C4—C5—H5	119.9	C15—C16—H16C	109.5
C4—C5—C6	120.18 (17)	H16A—C16—H16B	109.5
C6—C5—H5	119.9	H16A—C16—H16C	109.5
C1—C6—H6	120.3	H16B—C16—H16C	109.5
C5—C6—C1	119.39 (16)	C8—C17—H17A	109.5
C5—C6—H6	120.3	C8—C17—H17B	109.5
N1—C7—O3	116.20 (15)	C8—C17—H17C	109.5
N1—C7—C3	128.00 (16)	H17A—C17—H17B	109.5
O3—C7—C3	115.78 (15)	H17A—C17—H17C	109.5
N2—C8—C9	111.26 (13)	H17B—C17—H17C	109.5
N2—C8—C17	112.74 (15)	N2—C18—C19	116.33 (16)
O3—C8—N2	99.24 (12)	O4—C18—N2	120.39 (17)
O3—C8—C9	109.17 (13)	O4—C18—C19	123.28 (16)
O3—C8—C17	108.06 (14)	C18—C19—H19A	109.5
C17—C8—C9	115.09 (15)	C18—C19—H19B	109.5
C10—C9—C8	120.38 (15)	C18—C19—H19C	109.5
C10—C9—C14	118.86 (17)	H19A—C19—H19B	109.5
C14—C9—C8	120.64 (15)	H19A—C19—H19C	109.5
C9—C10—H10	119.6	H19B—C19—H19C	109.5
C11—C10—C9	120.80 (17)		

I1—C1—C2—C3	177.52 (12)	C6—C1—C2—C3	0.2 (3)
I1—C1—C6—C5	−178.17 (13)	C7—N1—N2—C8	7.40 (18)
F1—C12—C13—C14	177.44 (17)	C7—N1—N2—C18	−175.13 (15)
O1—C4—C5—C6	−176.19 (16)	C7—O3—C8—N2	11.41 (16)
N1—N2—C8—O3	−11.66 (16)	C7—O3—C8—C9	−105.04 (15)
N1—N2—C8—C9	103.18 (15)	C7—O3—C8—C17	129.12 (15)
N1—N2—C8—C17	−125.79 (15)	C7—C3—C4—O1	−7.2 (2)
N1—N2—C18—O4	−177.18 (15)	C7—C3—C4—C5	176.30 (16)
N1—N2—C18—C19	2.7 (2)	C8—N2—C18—O4	−0.1 (3)
C1—C2—C3—C4	0.8 (2)	C8—N2—C18—C19	179.75 (15)
C1—C2—C3—C7	−176.69 (15)	C8—O3—C7—N1	−8.6 (2)
N2—N1—C7—O3	0.70 (19)	C8—O3—C7—C3	169.74 (14)
N2—N1—C7—C3	−177.36 (16)	C8—C9—C10—C11	173.47 (17)
N2—C8—C9—C10	−90.33 (18)	C8—C9—C14—C13	−173.28 (16)
N2—C8—C9—C14	85.57 (19)	C9—C10—C11—C12	0.2 (3)
C2—C1—C6—C5	−0.9 (3)	C10—C9—C14—C13	2.7 (3)
C2—C3—C4—O1	175.43 (14)	C10—C11—C12—F1	−177.25 (18)
C2—C3—C4—C5	−1.0 (2)	C10—C11—C12—C13	2.1 (3)
C2—C3—C7—N1	178.95 (17)	C11—C12—C13—C14	−1.9 (3)
C2—C3—C7—O3	0.9 (2)	C12—C13—C14—C9	−0.6 (3)

O3—C8—C9—C10	18.2 (2)	C14—C9—C10—C11	−2.5 (3)
O3—C8—C9—C14	−165.92 (15)	C15—O1—C4—C3	81.4 (2)
C3—C4—C5—C6	0.3 (3)	C15—O1—C4—C5	−102.02 (18)
C4—O1—C15—O2	5.6 (2)	C17—C8—C9—C10	139.87 (17)
C4—O1—C15—C16	−176.14 (14)	C17—C8—C9—C14	−44.2 (2)
C4—C3—C7—N1	1.6 (3)	C18—N2—C8—O3	170.99 (15)
C4—C3—C7—O3	−176.45 (15)	C18—N2—C8—C9	−74.2 (2)
C4—C5—C6—C1	0.6 (3)	C18—N2—C8—C17	56.9 (2)

Hydrogen-bond geometry (Å, º)

*Cg*3 is the centroid of the C9–C14 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C5—H5···O4^{i}	0.95	2.53	3.331 (2)	142
C14—H14···O2^{ii}	0.95	2.51	3.335 (2)	145
C16—H16*A*···O4^{iii}	0.98	2.54	3.513 (2)	174
C17—H17*C*···*Cg*3^{ii}	0.98	2.50	3.407 (2)	154

Symmetry codes: (i) −*x*+1, *y*−1/2, −*z*+1/2; (ii) *x*, −*y*+3/2, *z*+1/2; (iii) *x*, −*y*+3/2, *z*−1/2.

2-[4-Acetyl-5-(4-chlorophenyl)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl]-4-iodophenyl acetate (6e)

Crystal data

$C_{19}H_{16}ClIN_2O_4$
M_r = 498.69
Monoclinic, $P2_1/c$
a = 11.703 (2) Å
b = 22.037 (4) Å
c = 7.4073 (12) Å
β = 92.888 (8)°
V = 1907.9 (5) Å^3
Z = 4
$F(000)$ = 984
D_x = 1.736 Mg m^{-3}
Mo $K\alpha$ radiation, λ = 0.71073 Å
Cell parameters from 9499 reflections
θ = 2.9–31.1°
μ = 1.85 mm^{-1}
T = 100 K
Block, colourless
0.22 × 0.12 × 0.12 mm

Data collection

Bruker APEXII CCD diffractometer
φ and ω scans
Absorption correction: multi-scan SADABS2014/2 (Bruker, 2014)
T_{min} = 0.640, T_{max} = 0.746
62840 measured reflections
4387 independent reflections
3863 reflections with $I > 2\sigma(I)$
R_{int} = 0.042
θ_{max} = 27.5°, θ_{min} = 2.9°
h = −15→15
k = −28→28
l = −9→9

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.021
$wR(F^2)$ = 0.051
S = 1.04
4387 reflections
247 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0233P)^2 + 1.3951P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.40 e Å^{-3}
$\Delta\rho_{min}$ = −0.66 e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
I1	0.89006 (2)	0.30547 (2)	0.88485 (2)	0.03207 (5)
Cl1	0.06374 (4)	0.34278 (2)	0.41999 (8)	0.03241 (12)
O1	0.77394 (10)	0.50823 (5)	0.31612 (16)	0.0169 (2)
N1	0.64395 (12)	0.42152 (6)	0.12176 (18)	0.0155 (3)
C1	0.84397 (15)	0.37358 (8)	0.6975 (2)	0.0175 (3)
O2	0.91227 (11)	0.47025 (6)	0.14881 (17)	0.0219 (3)
N2	0.56147 (13)	0.38760 (6)	0.02279 (19)	0.0165 (3)
C2	0.77370 (14)	0.35965 (7)	0.5465 (2)	0.0156 (3)
H2	0.742501	0.320035	0.532421	0.019*
O3	0.61627 (10)	0.33434 (5)	0.27089 (16)	0.0156 (2)
C3	0.74881 (14)	0.40416 (7)	0.4147 (2)	0.0135 (3)
O4	0.44240 (12)	0.37370 (6)	−0.22008 (18)	0.0279 (3)
C4	0.79720 (14)	0.46180 (7)	0.4405 (2)	0.0147 (3)
C5	0.86500 (15)	0.47563 (8)	0.5935 (2)	0.0176 (3)
H5	0.895568	0.515324	0.609208	0.021*
C6	0.88836 (15)	0.43149 (8)	0.7241 (2)	0.0183 (3)
H6	0.934058	0.440805	0.830114	0.022*
C7	0.67047 (14)	0.38903 (7)	0.2610 (2)	0.0137 (3)
C8	0.53275 (14)	0.33051 (7)	0.1187 (2)	0.0145 (3)
C9	0.41367 (14)	0.33227 (7)	0.1917 (2)	0.0142 (3)
C10	0.39456 (15)	0.36749 (8)	0.3436 (2)	0.0193 (4)
H10	0.456042	0.389965	0.399203	0.023*
C11	0.28763 (16)	0.37029 (8)	0.4149 (2)	0.0209 (4)
H11	0.275442	0.394248	0.518796	0.025*
C12	0.19911 (15)	0.33766 (8)	0.3323 (2)	0.0191 (4)
C13	0.21483 (16)	0.30168 (8)	0.1829 (3)	0.0226 (4)
H13	0.152988	0.279055	0.129009	0.027*
C14	0.32285 (16)	0.29914 (8)	0.1126 (2)	0.0198 (4)
H14	0.334764	0.274592	0.009782	0.024*
C15	0.84064 (15)	0.50789 (8)	0.1683 (2)	0.0172 (3)
C16	0.81145 (19)	0.56051 (9)	0.0475 (3)	0.0292 (4)
H16A	0.801965	0.596984	0.120947	0.044*
H16B	0.740015	0.552037	−0.022698	0.044*
H16C	0.873208	0.567020	−0.034917	0.044*
C17	0.55813 (15)	0.27428 (8)	0.0106 (2)	0.0197 (4)
H17A	0.548298	0.238187	0.085534	0.029*
H17B	0.637073	0.276005	−0.027385	0.029*
H17C	0.505453	0.272232	−0.096334	0.029*
C18	0.51525 (15)	0.40515 (8)	−0.1420 (2)	0.0190 (4)

C19	0.55873 (17)	0.46367 (9)	−0.2175 (2)	0.0239 (4)
H19A	0.516126	0.473014	−0.331441	0.036*
H19B	0.640246	0.459579	−0.239569	0.036*
H19C	0.548147	0.496532	−0.130830	0.036*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
I1	0.02554 (8)	0.03502 (8)	0.03427 (8)	−0.00758 (5)	−0.01207 (5)	0.02000 (6)
Cl1	0.0206 (2)	0.0319 (3)	0.0460 (3)	0.00113 (19)	0.0134 (2)	−0.0002 (2)
O1	0.0224 (6)	0.0132 (5)	0.0153 (6)	0.0002 (5)	0.0019 (5)	0.0013 (4)
N1	0.0162 (7)	0.0158 (7)	0.0143 (7)	−0.0012 (5)	−0.0003 (5)	−0.0009 (5)
C1	0.0145 (8)	0.0224 (9)	0.0156 (8)	−0.0002 (7)	0.0005 (6)	0.0049 (7)
O2	0.0227 (7)	0.0242 (7)	0.0192 (6)	−0.0005 (5)	0.0047 (5)	0.0013 (5)
N2	0.0183 (7)	0.0169 (7)	0.0140 (7)	−0.0030 (6)	−0.0019 (6)	0.0012 (5)
C2	0.0144 (8)	0.0151 (8)	0.0174 (8)	−0.0022 (6)	0.0011 (6)	0.0005 (6)
O3	0.0157 (6)	0.0147 (6)	0.0158 (6)	−0.0030 (5)	−0.0048 (5)	0.0014 (4)
C3	0.0114 (8)	0.0156 (8)	0.0135 (7)	−0.0004 (6)	0.0018 (6)	−0.0005 (6)
O4	0.0291 (8)	0.0343 (8)	0.0191 (7)	−0.0041 (6)	−0.0088 (6)	0.0005 (6)
C4	0.0152 (8)	0.0155 (8)	0.0137 (8)	0.0010 (6)	0.0034 (6)	0.0007 (6)
C5	0.0190 (9)	0.0168 (8)	0.0173 (8)	−0.0037 (7)	0.0030 (7)	−0.0032 (6)
C6	0.0149 (8)	0.0259 (9)	0.0141 (8)	−0.0037 (7)	0.0001 (6)	−0.0018 (7)
C7	0.0130 (8)	0.0131 (7)	0.0152 (8)	−0.0004 (6)	0.0026 (6)	−0.0010 (6)
C8	0.0150 (8)	0.0156 (8)	0.0125 (8)	−0.0013 (6)	−0.0023 (6)	−0.0004 (6)
C9	0.0165 (8)	0.0127 (7)	0.0131 (8)	0.0012 (6)	−0.0018 (6)	0.0009 (6)
C10	0.0196 (9)	0.0206 (8)	0.0174 (8)	−0.0013 (7)	−0.0018 (7)	−0.0049 (7)
C11	0.0243 (9)	0.0205 (9)	0.0179 (9)	0.0040 (7)	0.0023 (7)	−0.0044 (7)
C12	0.0158 (8)	0.0188 (8)	0.0231 (9)	0.0027 (7)	0.0047 (7)	0.0055 (7)
C13	0.0176 (9)	0.0226 (9)	0.0273 (10)	−0.0036 (7)	−0.0012 (7)	−0.0031 (7)
C14	0.0197 (9)	0.0207 (9)	0.0189 (8)	−0.0012 (7)	−0.0008 (7)	−0.0062 (7)
C15	0.0180 (8)	0.0179 (8)	0.0155 (8)	−0.0062 (7)	−0.0002 (7)	0.0010 (6)
C16	0.0346 (11)	0.0273 (10)	0.0258 (10)	−0.0006 (8)	0.0021 (8)	0.0121 (8)
C17	0.0191 (9)	0.0193 (8)	0.0208 (9)	0.0004 (7)	0.0023 (7)	−0.0054 (7)
C18	0.0196 (9)	0.0228 (9)	0.0146 (8)	0.0048 (7)	0.0011 (7)	−0.0002 (7)
C19	0.0308 (10)	0.0254 (9)	0.0156 (9)	0.0029 (8)	0.0022 (7)	0.0053 (7)

Geometric parameters (Å, º)

I1—C1	2.0963 (17)	C8—C17	1.513 (2)
Cl1—C12	1.7459 (18)	C9—C10	1.395 (2)
O1—C4	1.395 (2)	C9—C14	1.394 (2)
O1—C15	1.377 (2)	C10—H10	0.9500
N1—N2	1.399 (2)	C10—C11	1.384 (3)
N1—C7	1.281 (2)	C11—H11	0.9500
C1—C2	1.389 (2)	C11—C12	1.379 (3)
C1—C6	1.388 (2)	C12—C13	1.381 (3)
O2—C15	1.193 (2)	C13—H13	0.9500
N2—C8	1.491 (2)	C13—C14	1.392 (3)

N2—C18	1.366 (2)	C14—H14	0.9500
C2—H2	0.9500	C15—C16	1.493 (2)
C2—C3	1.404 (2)	C16—H16A	0.9800
O3—C7	1.366 (2)	C16—H16B	0.9800
O3—C8	1.4568 (19)	C16—H16C	0.9800
C3—C4	1.400 (2)	C17—H17A	0.9800
C3—C7	1.464 (2)	C17—H17B	0.9800
O4—C18	1.221 (2)	C17—H17C	0.9800
C4—C5	1.384 (2)	C18—C19	1.505 (3)
C5—H5	0.9500	C19—H19A	0.9800
C5—C6	1.389 (2)	C19—H19B	0.9800
C6—H6	0.9500	C19—H19C	0.9800
C8—C9	1.520 (2)		

C15—O1—C4	114.96 (13)	C11—C10—H10	119.4
C7—N1—N2	104.84 (14)	C10—C11—H11	120.6
C2—C1—I1	119.80 (13)	C12—C11—C10	118.76 (16)
C6—C1—I1	118.83 (13)	C12—C11—H11	120.6
C6—C1—C2	121.32 (16)	C11—C12—Cl1	118.47 (14)
N1—N2—C8	111.55 (13)	C11—C12—C13	121.84 (16)
C18—N2—N1	123.28 (14)	C13—C12—Cl1	119.69 (14)
C18—N2—C8	125.17 (14)	C12—C13—H13	120.6
C1—C2—H2	120.0	C12—C13—C14	118.87 (17)
C1—C2—C3	119.95 (15)	C14—C13—H13	120.6
C3—C2—H2	120.0	C9—C14—H14	119.7
C7—O3—C8	107.76 (12)	C13—C14—C9	120.60 (16)
C2—C3—C7	118.79 (15)	C13—C14—H14	119.7
C4—C3—C2	118.07 (15)	O1—C15—C16	110.52 (15)
C4—C3—C7	123.10 (15)	O2—C15—O1	122.00 (15)
O1—C4—C3	120.76 (15)	O2—C15—C16	127.46 (17)
C5—C4—O1	117.65 (15)	C15—C16—H16A	109.5
C5—C4—C3	121.53 (15)	C15—C16—H16B	109.5
C4—C5—H5	120.0	C15—C16—H16C	109.5
C4—C5—C6	120.03 (16)	H16A—C16—H16B	109.5
C6—C5—H5	120.0	H16A—C16—H16C	109.5
C1—C6—C5	119.06 (16)	H16B—C16—H16C	109.5
C1—C6—H6	120.5	C8—C17—H17A	109.5
C5—C6—H6	120.5	C8—C17—H17B	109.5
N1—C7—O3	116.24 (15)	C8—C17—H17C	109.5
N1—C7—C3	128.02 (15)	H17A—C17—H17B	109.5
O3—C7—C3	115.71 (14)	H17A—C17—H17C	109.5
N2—C8—C9	112.35 (14)	H17B—C17—H17C	109.5
N2—C8—C17	112.57 (14)	N2—C18—C19	116.68 (16)
O3—C8—N2	99.28 (12)	O4—C18—N2	119.87 (16)
O3—C8—C9	108.34 (13)	O4—C18—C19	123.46 (16)
O3—C8—C17	108.37 (13)	C18—C19—H19A	109.5
C17—C8—C9	114.64 (14)	C18—C19—H19B	109.5
C10—C9—C8	119.22 (15)	C18—C19—H19C	109.5

C14—C9—C8	122.03 (15)	H19A—C19—H19B	109.5
C14—C9—C10	118.74 (16)	H19A—C19—H19C	109.5
C9—C10—H10	119.4	H19B—C19—H19C	109.5
C11—C10—C9	121.16 (16)		

I1—C1—C2—C3	−175.79 (12)	C6—C1—C2—C3	1.7 (3)
I1—C1—C6—C5	175.24 (13)	C7—N1—N2—C8	2.98 (18)
Cl1—C12—C13—C14	178.69 (14)	C7—N1—N2—C18	−176.27 (16)
O1—C4—C5—C6	178.30 (15)	C7—O3—C8—N2	5.51 (15)
N1—N2—C8—O3	−5.26 (16)	C7—O3—C8—C9	−111.89 (14)
N1—N2—C8—C9	109.07 (15)	C7—O3—C8—C17	123.16 (14)
N1—N2—C8—C17	−119.69 (15)	C7—C3—C4—O1	−1.2 (2)
N1—N2—C18—O4	−179.05 (16)	C7—C3—C4—C5	175.70 (15)
N1—N2—C18—C19	0.9 (2)	C8—N2—C18—O4	1.8 (3)
C1—C2—C3—C4	0.4 (2)	C8—N2—C18—C19	−178.20 (15)
C1—C2—C3—C7	−177.32 (15)	C8—O3—C7—N1	−4.56 (19)
N2—N1—C7—O3	0.98 (19)	C8—O3—C7—C3	173.32 (13)
N2—N1—C7—C3	−176.59 (16)	C8—C9—C10—C11	−179.82 (16)
N2—C8—C9—C10	−74.07 (19)	C8—C9—C14—C13	179.91 (16)
N2—C8—C9—C14	106.70 (18)	C9—C10—C11—C12	−0.3 (3)
C2—C1—C6—C5	−2.3 (3)	C10—C9—C14—C13	0.7 (3)
C2—C3—C4—O1	−178.77 (14)	C10—C11—C12—Cl1	−178.58 (14)
C2—C3—C4—C5	−1.9 (2)	C10—C11—C12—C13	1.1 (3)
C2—C3—C7—N1	−174.43 (16)	C11—C12—C13—C14	−1.0 (3)
C2—C3—C7—O3	8.0 (2)	C12—C13—C14—C9	0.1 (3)
O3—C8—C9—C10	34.6 (2)	C14—C9—C10—C11	−0.6 (3)
O3—C8—C9—C14	−144.63 (15)	C15—O1—C4—C3	−83.54 (19)
C3—C4—C5—C6	1.3 (3)	C15—O1—C4—C5	99.47 (17)
C4—O1—C15—O2	0.4 (2)	C17—C8—C9—C10	155.75 (16)
C4—O1—C15—C16	−178.08 (15)	C17—C8—C9—C14	−23.5 (2)
C4—C3—C7—N1	8.0 (3)	C18—N2—C8—O3	173.97 (15)
C4—C3—C7—O3	−169.58 (15)	C18—N2—C8—C9	−71.7 (2)
C4—C5—C6—C1	0.8 (3)	C18—N2—C8—C17	59.5 (2)

Hydrogen-bond geometry (Å, º)

*Cg*2 is the centroid of the C1–C6 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6···O2^{i}	0.95	2.47	3.258 (2)	140
C11—H11···O1^{ii}	0.95	2.55	3.435 (2)	155
C19—H19*B*···*Cg*2^{iii}	0.98	2.75	3.649 (2)	153

Symmetry codes: (i) *x*, *y*, *z*+1; (ii) −*x*+1, −*y*+1, −*z*+1; (iii) *x*, *y*, *z*−1.