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Methyl 2-(4-bromophenyl)-1-(5-*tert*-butyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole-5-carboxylate: a hydrogen-bonded chain of edge-fused centrosymmetric rings

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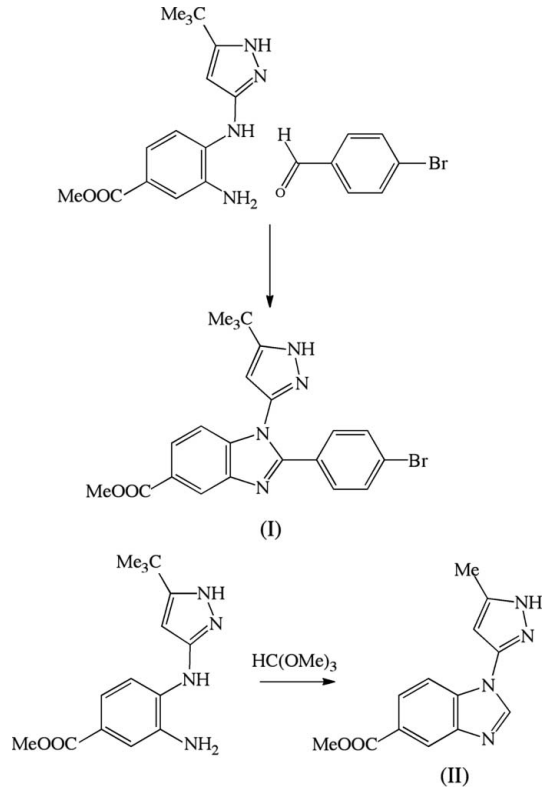
In the title compound, $C_{22}H_{21}BrN_4O_2$, the imidazole and pyrazole rings are almost orthogonal to each other, but the ester unit is effectively coplanar with the adjacent aryl rings. The molecules are linked into a chain of edge-fused centrosymmetric rings by a combination of N—H···O and C—H···π(arene) hydrogen bonds.

Comment

The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds (Adams *et al.*, 1998). In particular, the benzimidazole unit may be considered structurally isosteric with the purine unit of nucleotides, so that this unit can readily interact with biopolymers, thus conferring potential activity for chemotherapeutic applications upon compounds containing the benzimidazole unit (Ören *et al.*, 1998). The pyrazole core is also frequently found in compounds with significant biological activity (Park *et al.*, 2005; Insuasty *et al.*, 2008). As part of a synthetic programme aimed at the development of antitumour compounds containing a combination of benzimidazole and pyrazole units, we have now prepared methyl 2-(4-bromophenyl)-1-(5-*tert*-butyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole-5-carboxylate, (I) (Fig. 1), using an oxidative cyclocondensation of an *ortho*-diaminobenzene derivative, having a pyrazole residue linked to one amino group, with an arylaldehyde, in this case the condensation between methyl 3-amino-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)benzoate and 4-bromobenzaldehyde. Although similar oxidative cyclocondensation routes to benzimidazoles have been reported recently, these all involve reactions in solution, as opposed to the solvent-free procedure employed here, and, in general, involve the addition of specific oxidizing agents to the reaction medium (Bressi *et al.*, 2010; Murai *et al.*, 2010; Tonelli *et al.*, 2010), whereas no such oxidant was required for the high-yield synthesis of (I). We report here the molecular and supramolecular structure of (I), which we compare with the related compound methyl 1-(5-methyl-1*H*-pyrazol-3-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate, (II), which was prepared using a rather similar synthetic approach, namely a simple cyclocondensation of methyl 3-amino-4-[(5-methyl-1*H*-pyrazole-3-yl)amino]benzoate with trimethyl orthoformate (Portilla *et al.*, 2007).



The molecular conformation of (I) is dominated by the dihedral angles between the plane of the imidazole ring and those of the pyrazole and brominated aryl rings. These dihedral angles are 83.30 (15) and 26.90 (14)°, respectively, and the near orthogonality of the imidazole and pyrazole rings presents a marked contrast with the conformation adopted by (II) (Portilla *et al.*, 2007). Compound (II) crystallizes with $Z' = 2$ in the space group $P\overline{1}$, as opposed to $Z' = 1$ in the space group $P2_1/c$ for (I), and the dihedral angles between the planes of the imidazole and pyrazole rings in the two independent molecules are 5.5 (2) and 5.9 (2)°, so that the ring systems in the molecules of (II) are very nearly planar. By contrast, the ester groups in (II) are both rotated out of the planes of the adjacent aryl rings by *ca* 15°, whereas the ester group in (I) is effectively coplanar with the adjacent aryl ring; the maximum deviations of the non-H atoms in the ester group of (I) from the mean plane of the adjacent aryl ring occur for the two O atoms, each displaced by only 0.068 (2) Å, as the relevant torsion angles confirm (Table 1). Finally, the *tert*-butyl group adopts a conformation in which the projection of the C16—C19 bond is almost orthogonal to the pyrazole plane. The

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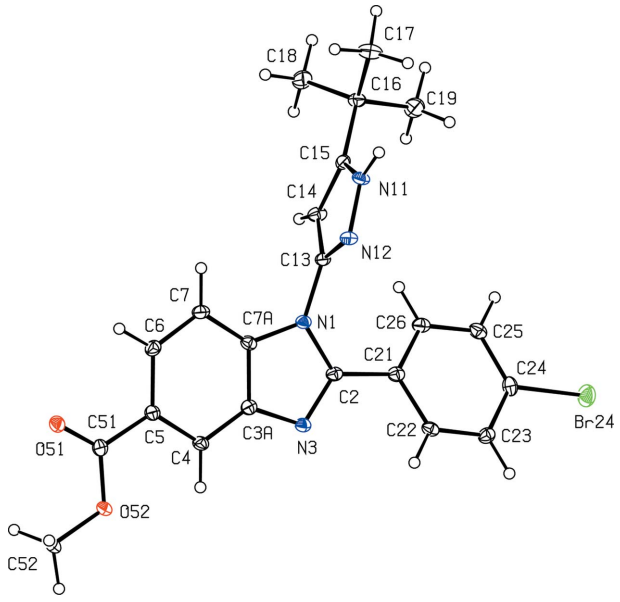

Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

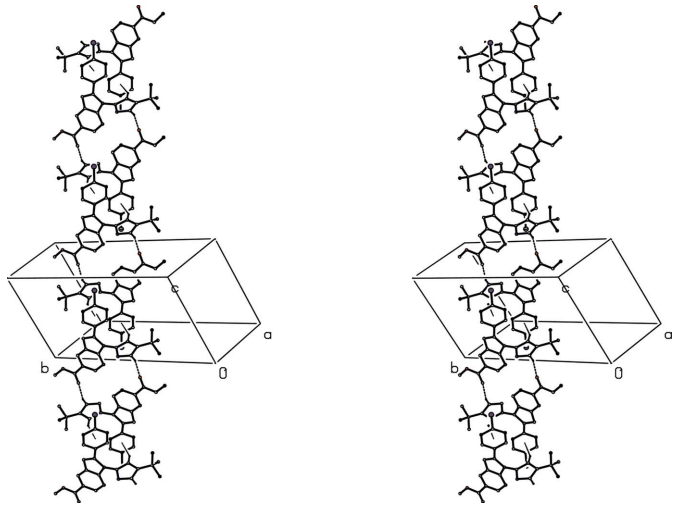

Figure 2
A stereoview of part of the crystal structure of (I), showing the formation of a hydrogen-bonded chain of edge-fused centrosymmetric rings running parallel to the [101] direction. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

molecule of (I) has no internal symmetry and hence it is conformationally chiral. However, the centrosymmetric space group accommodates equal numbers of the two conformational enantiomers.

The conformational differences between the molecules of (I) and (II) cannot plausibly be interpreted in terms of intramolecular factors only. More probably, they are determined primarily by the different direction-specific intermolecular forces which are manifest in the two crystal structures, in particular, the different hydrogen-bonding patterns, which involve both the pyrazole ring and the ester unit in each compound, and which are discussed below.

There is strong bond fixation within the imidazole ring in (I), as exemplified by the C2—N3 and N3—C3a distances (Table 1). In the adjacent aryl ring, the longest of the peripheral C—C bonds is C5—C6, while the exocyclic C5—C51 bond is short for its type [mean value (Allen *et al.*, 1987) = 1.487 Å and lower-quartile value = 1.480 Å]. However, the remaining bond distances provide no evidence for any significant polarization or charge separation in the molecular fragment between atoms N1 and O51.

The molecules of (I) are linked by a combination of N—H···O and C—H···π(arene) hydrogen bonds (Table 2). However, despite the presence within the molecule of two essentially unencumbered aryl rings, aromatic π–π stacking interactions are absent from the crystal structure of (I), nor are there any short intermolecular contacts involving pairs of Br atoms (Ramasubbu *et al.*, 1986). It is convenient to consider first the actions of the two independent hydrogen bonds, and then their action in combination. Pyrazole ring atom N11 at (x, y, z) acts as hydrogen-bond donor to carbonyl atom O51 in the molecule at ($1-x$, $1-y$, $2-z$), so forming a cyclic centrosymmetric $R_2^2(22)$ (Bernstein *et al.*, 1995) ring centred at ($\frac{1}{2}$, $\frac{1}{2}$, 1). Pyrazole ring atom C14 at (x, y, z) acts as hydrogen-bond donor to the brominated aryl ring C21–C26 in the molecule at ($-x$, $1-y$, $1-z$), so forming a second cyclic centrosymmetric motif this time centred at (0, $\frac{1}{2}$, $\frac{1}{2}$). The combination of these two ring motifs, and their propagation by inversion, leads to the formation of a chain of edge-fused rings running parallel to the [101] direction, in which the rings formed by pairs of N—H···O hydrogen bonds are centred at ($n+\frac{1}{2}$, $\frac{1}{2}$, $n+1$), where n represents an integer, while the rings formed by pairs of C—H···π(arene) hydrogen bonds are centred at (n, $\frac{1}{2}$, $n+\frac{1}{2}$), where n again represents an integer (Fig. 2).

The hydrogen bonds present in (I) and the resulting supramolecular structure provide an interesting contrast with those in (II) (Portilla *et al.*, 2007). As noted above, (II) crystallizes with $Z'=2$ and each of the independent molecules forms an independent hydrogen-bonded substructure. Each of the two types of molecule in (II) participates in one N—H···N and one C—H···O hydrogen bond, in which the donors are both components of the pyrazole ring, as in (I), while the acceptors are, respectively, the two-coordinated N atom of the imidazole ring and the carbonyl O atom. Each type of molecule in (II) then forms a hydrogen-bonded sheet containing a single type of $R_4^4(28)$ ring and in which the component molecules are all related to one another by translation. There are no direction-specific interactions between the two types of sheets, which are stacked alternately along [001], and, in particular, there are no direction-specific interactions between the two independent molecules.

Compounds (I) and (II) thus differ, despite their similar molecular constitutions, in their crystallization characteristics (space groups and Z' values), in their molecular conformations, in their hydrogen bonds, where the same two donors are present but involved with different sets of acceptors, and in their overall hydrogen-bonded structures, *viz.* a chain of fused rings in (I) and two independent sheets in (II).

Experimental

A mixture of methyl 3-amino-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)-benzoate (1 mmol) and 4-bromobenzaldehyde (1.2 mmol) was heated at 413 K in the absence of solvent for 2 h. After the complete disappearance of the starting material (as monitored by thin-layer chromatography), the mixture was cooled to ambient temperature and the crude product was purified by column chromatography on silica gel using a chloroform–methanol (40:1 *v*/*v*) mixture as eluent, to afford the title compound, (I). Slow evaporation of the solution in chloroform–methanol at ambient temperature and in air gave colourless crystals of (I) suitable for single-crystal X-ray diffraction (yield 92%, m.p. 534 K). MS (70 eV, EI) *m*/*z* (%): 454/452 (100/98, M^+), 439/437 [24/24, $(M - CH_3)^+$], 423/421 [25/25, $(M - OCH_3)^+$], 397 (11), 395 (14). Analysis found: C 58.2, H 4.8, N 12.3%; $C_{22}H_{21}BrN_4O_2$ requires: C 58.3, H 4.7, N 12.4%.

Crystal data

$C_{22}H_{21}BrN_4O_2$
M_r = 453.33
Monoclinic, $P2_1/c$
a = 8.1296 (15) Å
b = 22.187 (3) Å
c = 11.152 (3) Å
β = 102.222 (18)°
V = 1965.9 (7) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 2.12 mm^{-1}
T = 120 K
0.28 × 0.20 × 0.18 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.589, T_{max} = 0.683
30453 measured reflections
4516 independent reflections
3190 reflections with $I > 2\sigma(I)$
R_{int} = 0.063

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.083
S = 1.05
4516 reflections
266 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.53 e Å^{-3}
$\Delta\rho_{min}$ = −0.59 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.383 (3)	C6—C7	1.367 (4)
C2—N3	1.300 (3)	C7—C7a	1.376 (4)
N3—C3a	1.379 (3)	C7a—N1	1.368 (3)
C3a—C4	1.377 (3)	C3a—C7a	1.394 (3)
C4—C5	1.386 (4)	C5—C51	1.466 (4)
C5—C6	1.398 (3)	C51—O51	1.205 (3)
N11—C15—C16—C17	−22.1 (4)	C4—C5—C51—O51	179.3 (2)
N11—C15—C16—C18	−143.4 (2)	C4—C5—C51—O52	−1.0 (3)
N11—C15—C16—C19	97.3 (3)	C5—C51—O52—C52	−176.4 (2)

All H atoms were located in a difference map and then treated as riding atoms in geometrically idealized positions, with C—H = 0.95 (ring C—H) or 0.98 Å (methyl) and N—H = 0.88 Å, and with U_{iso}(H) = kU_{eq}(carrier), where k = 1.5 for the methyl groups, which were permitted to rotate but not to tilt, or 1.2 for all other H atoms.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *DIRAX*/*LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97* and *PLATON*.

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

Cg is the centroid of the C21–C26 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N11—H11···O51^{i}	0.88	2.01	2.839 (3)	156
C14—H14···*Cg*^{ii}	0.95	2.63	3.492 (3)	153

Symmetry codes: (i) $-x+1, -y+1, -z+2$; (ii) $-x, -y+1, -z+1$.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3398). Services for accessing these data are described at the back of the journal.

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