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Crystal structure of (3-(dimethoxymethyl)-5-methoxy-1*H*-indol-1-yl) (2-iodo-5-methoxyphenyl) methanone, C₂₀H₂₀INO₅

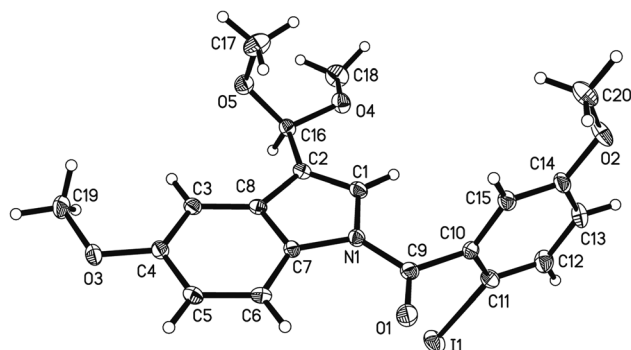


Table 1: Data collection and handling.

Crystal:	Clear light colourless block
Size:	0.14 × 0.13 × 0.10 mm
Wavelength:	CuKα radiation (1.54178 Å)
μ:	13.5 mm ⁻¹
Diffractometer, scan mode:	Rigaku synergy R, ω scan
θ _{max} , completeness:	73.4°, 100 %
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} , <i>R</i> _{int} :	13531, 3677, 0.064
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 2σ(<i>I</i> _{obs}), 3,546
<i>N</i> (param) _{refined} :	248
Programs:	RIGAKU, ¹ SHELX ^{2,3}

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Abstract

C₂₀H₂₀INO₅, monoclinic, *P*₂/c (no. 14), *a* = 14.49960(10) Å, *b* = 18.5114(2) Å, *c* = 7.09190(10) Å, β = 95.2400(10)°, *V* = 1895.57(4) Å³, *Z* = 4, *R*_{gt}(*F*) = 0.0348, *wR*_{ref}(*F*²) = 0.0913, *T* = 293(2) K.

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The crystal structure is shown in figure. Displacement ellipsoids are drawn at the 30 % probability level. Table 1 contains the crystallographic data and the list of the atoms including atomic coordinates and displacement parameters can be found in the cif-file attached to this article.

1 Source of material

The target compound (3-(dimethoxymethyl)-5-methoxy-1*H*-indol-1-yl)(2-iodo-5-methoxyphenyl)methanone was

synthesized via acylation of 3-(dimethoxymethyl)-5-methoxy-1*H*-indole with the corresponding acyl chloride. A 50 mL round-bottomed flask was charged with sodium hydride (684 mg, 17.1 mmol) and anhydrous *N,N*-dimethylformamide (DMF, 7 mL). The mixture was stirred in an ice-water bath for 5 min. Subsequently, a solution of 3-(dimethoxymethyl)-5-methoxy-1*H*-indole (840 mg, 3.8 mmol) in anhydrous DMF (5 mL) was added dropwise to the reaction system. Upon completion of the addition, stirring was continued for an additional 5 min. Thereafter, a pre-prepared solution of 2-iodo-5-methoxybenzoyl chloride (2,475 mg, 8.36 mmol) in anhydrous DMF (5 mL) was added dropwise. Following the complete addition, the reaction mixture was gradually warmed to room temperature and stirred for 5 h. The progress of the reaction was monitored by thin-layer chromatography (TLC) using UV detection at 254 nm. Upon completion of the reaction, the mixture was carefully quenched with a saturated ammonium chloride solution, resulting in the precipitation of the crude product. The crude product was triturated with petroleum ether/ethyl acetate (1:1, v/v), followed by filtration and washing to afford the pure product (1,426 mg, yield 78 %). Crystals were obtained by recrystallization from a *n*-hexane/ethyl acetate (1:1, v/v) solution.

2 Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms, with *d* (C–H) = 0.96 Å (methyl), *U*_{iso}(H) = 1.5*U*_{eq}(C), and *d*(C–H) = 0.98 Å (methyne),

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$$U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C}), \text{ and } d(\text{C}-\text{H}) = 0.93 \text{ \AA} \text{ (aromatic),}$$

$$U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C}).$$

3 Comment

Nitrogen-containing heterocycles are ubiquitous in bioactive molecules and pharmaceutical compounds.⁴ In structural optimization of drug molecules, replacing the original benzene ring with aromatic nitrogen-containing heterocycles like pyridine, pyrimidine, pyrrole, pyrazole,⁵ as well as substituting the naphthalene ring with quinoline or indole,⁶ have become one of the most common modification strategies. The above modification methods could achieve multiple objectives including enhanced biological activity, improved pharmacokinetic stability, increased water solubility, and circumvention of patent restrictions.^{7–9} On the other hand, consistent with principles of organic chemistry, the methoxy group acted as both a strong electron-donating group and a steric hindrance factor in electrophilic aromatic substitution reactions.¹⁰ It activated the aromatic ring through its electron-donating capability while simultaneously exerting steric control to direct the regiochemistry of electrophilic attack.¹¹ As one of the most prevalent substituents in bioactive molecular structures, methoxy groups were present in over 230 marketed small-molecule drugs.¹² Methoxy groups could form hydrogen bonds and hydrophobic interactions with target proteins,¹³ while exerting significant conformational regulation and restriction effects on molecules.¹⁴ Based on the above background, in our preliminary research,¹⁵ we designed and synthesized a series of *N*-acylindole compounds featuring dual methoxy substitutions. In this work, the crystals of (3-(dimethoxymethyl)-5-methoxy-1*H*-indol-1-yl)(2-iodo-5-methoxyphenyl)methanone were obtained and its structure is reported here.

Single-crystal X-ray diffraction analysis reveals that there is one molecule in the asymmetric unit (*cf.* the figure). All bond lengths and bond angles are within the typical range.^{16–18} In the target molecule, the iodine-substituted benzene ring and the indole ring are linked via a carbonyl group. Due to the conjugation between the N(1) atom of the indole moiety and the carbonyl group, the C(9)–N(1) bond length (1.385(3) Å) is significantly shorter than that of a normal C–N single bond, which is comparable to the C(1)–N(1) (1.405(3) Å) and C(7)–N(1) (1.411(3) Å) bonds within the indole ring. The torsion angles of O(1)–C(9)–N(1)–C(1) and O(1)–C(9)–N(1)–C(7) are 178.3(2)° and –5.0(4)°, respectively, indicating that the amide segment and the indole ring are nearly coplanar. This structural feature is presumably attributed to the conjugation effect and minimal steric hindrance. In contrast, the torsion angles of O(1)–C(9)–

C(10)–C(11) and O(1)–C(9)–C(10)–C(15) are 88.6(3)° and –91.0(3)°, respectively, suggesting that the carbonyl group and the benzene ring adopt an almost perpendicular conformation. This conformation is likely caused by steric repulsion between the carbonyl oxygen atom and the iodine atom. Overall, as a result of the aforementioned effects, the indole ring and the methoxy-substituted benzene ring are nearly perpendicular to each other, with a dihedral angle of 87.99(3)°.

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