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RESEARCH ARTICLE

DMF Solvated Structure of 3'-[(4-Fluorophenyl)-carbonyl]-5'-[2-(methylsulfanyl)ethyl]-4'-(phenyl)spiro[indole-3,2'-pyrrolidin]-2(1*H*)-one: A Pyrrolidine Alkaloidal Derivative

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Abstract: The compound 3'-[(4-fluorophenyl)carbonyl]-5'-[2-(methylsulfanyl)ethyl]4'-(phenyl) spiro[indole-3,2'-pyrrolidin]-2(1*H*)-one, $C_{30}H_{31}FN_3O_3S$, crystallizes in the orthorhombic space group $P2_12_12_1$ with unit cell parameters, a = 6.3529(8) Å, b = 11.4335(14) Å, c = 38.405(4) Å, $\alpha = \beta = \gamma = 90.0^o$, Z=4. The crystal structure was solved by direct methods. The data were collected at room temperature (293 K) and the structure was refined by full-matrix least-squares procedures to a final R-value of 0.1015 for 3630 observed reflections. The molecular structure is stabilized by one intra [C-H…O] and one DMF-guided inter [N-H…O] molecular interaction. Besides this, few C–H···π interactions have also been observed.

Keywords: Spiro-oxindole, Pyrrolidine, Direct method, Crystal structure, Intermolecular interactions

Introduction

Functionalized pyrrolidine, pyrrolizidine and oxindole alkaloids are important classes of synthetic targets as they possess significant biological activity[1]. Several natural alkaloids containing spiro-oxindole systems *e.g*., spirotryprostatin A, isopteropodine and pteropodine, which have shown important biological activity with potential use in antibacterial, antiprotozoal, and anticancer activities[2]. Thus spiro-oxindole / pyrrolidine framework forms an important structural motif in biologically relevant compounds and are characterized by highly pronounced biological properties[3-6]. Therefore, in view of the importance of alkaloidal derivatives of this kind, we report the synthesis and crystal structure of the title compound.

Experimental

The synthetic route for the title compound (Figure 1) is presented in Scheme 1. A mixture of isatin (0.01 mol, 1.4 g), methionine (0.01 mol, 1.49 g) and 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (0.01 mol, 2.26 g) in ethanol was refluxed for 24 h. After the completion of reaction, the reaction mixture was cooled to room temperature and quenched with ice cold water. The resulting precipitate was filtered and recrystallized from DMF (M.P. 441-443 K).

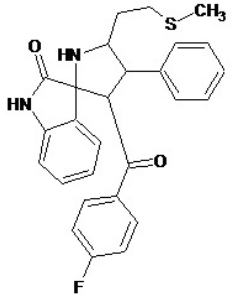
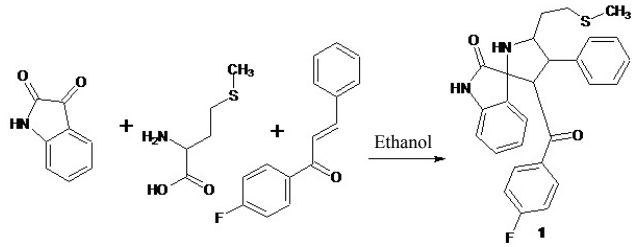


Figure 1. Chemical stucture of the title compound



Scheme 1. Synthesis of title compound

Crystal structure determination and refinement

The crystal of dimensions 0.30x0.20x0.20 mm used for data collection on *X*'calibur CCD area-detector diffractometer equipped with graphite monochromated Mo*Kα* radiation (λ=0.71073 Å)[7]. X-ray intensity data of 7276 reflections were collected at 293(2) K and out of these reflections 4877 were found unique. The intensities were measured by ω scan mode for θ ranges 3.56 to 25.99°. 3630 reflections were treated as observed using ($I>2\sigma(I)$) as criterion. Data were corrected for Lorentz-polarization and absorption factors. The structure was solved[8a] by direct methods using SHELXS97.

All non-hydrogen atoms of the molecule were located in the best E-map. All the hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-H atoms with C-H= 0.93-0.98 Å and U_{iso} = 1.2 U_{eq}(C), except for the methyl groups where U_{iso}(H) = 1.5U_{eq}(C). The final refinement cycles converged to an *R*- factor of 0.1015 (w*R* (F^2) = 0.2507) for the 3630 observed reflections. A relatively large value of the reliability index (R-factor) is due to the poor quality crystallization of the compounds. Efforts were made to achieve better quality crystallization with various solvent systems but DMF only could yield crystals for this compound. Residual electron densities ranges from -0.296 to 0.314 eÅ^{-3}. Atomic scattering factors were taken from International Tables for X-ray Crystallography[8b].

Results and Discussion

An ORTEP view of the title compound[9] with atomic labeling is shown in Figure 2. The geometry of the molecule was calculated using the PL ATON[10] and PARST[11] software. Crystal data, along with data collection and structure refinement details are summarized in Table 1. Selected bond lengths and angles are given in Table 2. The title compound consists of one oxindole ring, one pyrrolidine ring, three phenyl rings and DMF as a solvent molecule. All bond distances and bond angles in the title compound are within expected range and agree well with some related structure like 1'-(4-bromophenyl)-2'-[(4fluorophenyl) carbonyl]-1',2',5',6',7',7a'-hexahydrospiro[indole-3,3'-pyrrolizin]-2(1*H*)-one[12] and (3'-[(4-fluorophenyl)carbonyl]-5'-(hydroxymethyl)-4'-phenylspiro[indole-3,2'-pyrrolidin]-2(1*H*)-one[13].

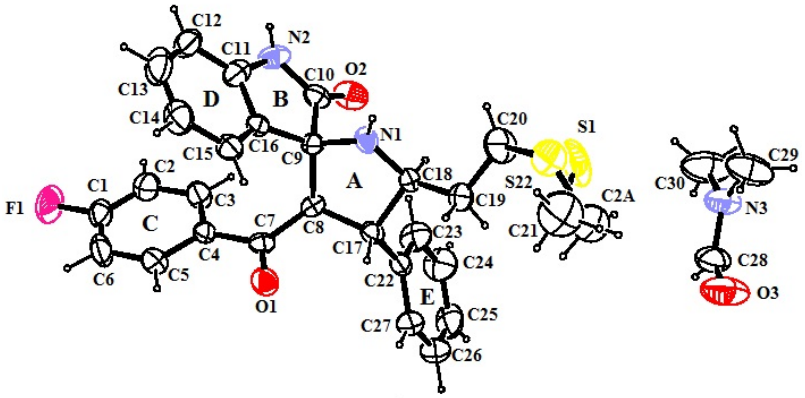


Figure 2. ORTEP view of the molecules with displacement ellipsoids drawn at 40% probabality lavel H atoms are shown as small spheres of arbitraty radii

Table 1. Crystal and experimental data

CCDC No.	1410401
Crystal size	0.30x0.20x0.20 mm
Empirical formula	C_{30} $H_{31}FN_3O_3S$
Formula weight	532.64
Radiation, Wavelength	Mo *Kα*, 0.71073 Å
Unit cell dimensions	a = 6.3529(8), b =11.4335(14), c = 38.405(4)Å β =90.00°
Crystal system	orthorhombic
Space group	P $2_12_12_1$
Unit cell volume	2789.6(6)Å^3
No. of molecules per unit cell, Z	4
Temperature	293(2)
Absorption coefficient	0.158 mm^{-1}
F(000)	1124
Scan mode	ω scan
θ range for entire data collection	3.56<θ< 25.99°
Range of indices	*h*= -7 to 7, *k*= -13 to 14, *l*= -16 to 47
Reflections collected / unique	7276 / 4877

Reflections observed (I > 2σ(I))	3630
R_{int}0.0487	
R_{sigma}0.0770	
No. of parameters refined	350
Final R	0.1015
wR(F^2)	0.2507
Goodness-of-fit	1.066
$(\Delta/\sigma)_{max}$	0.000
Final residual electron density	-0.296 to 0.314 eÅ^{-3}

Table 2. Selected bond lengths (Å) and bond angles (º) for non-hydrogen atoms (e.s.d.'s are given in parentheses)

Bond distance		Bond angle	
F1 - C1	1.370(8)	C9 - N1 - C18	106.5(5)
S1 - C21	1.81(2)	C10 - N2 - C11	111.5(6)
S22 - C2A	1.71(4)	C28 - N3 - C29	120.3(8)
O1 - C7	1.224(7)	C28 - N3 - C30	121.7(8)
O2 - C10	1.195(8)	C29 - N3 - C30	117.9(8)
O3 - C28	1.199(10)	C20 - S1 - C21	99.1(10)
N1 - C9	1.466(7)	C2A - S22 - C20	100(2)
N2 - C11	1.416(9)	C5 - C4 - C7 - O1	6.8(9)
N3 - C28	1.336(10)	C5 - C4 - C7 - C8	-170.8(6)
N3 - C29	1.448(11)	C7 - C8 - C9 - C16	-10.1(7)
N3 - C30	1.459(11)	C8 - C17 - C22 - C27	-115.0(7)
C20 - S22	1.838(13)	C17 - C18 - C19 - C20	177.4(7)
C20 - S1	1.778(9)	C8 - C9 - C16 - C15	64.1(9)

The double bond character of C7=O1, C10= O2 and O3=C28 are confirmed by their respective distances of 1.224(7) Å, 1.195(8) Å and 1.199(10) Å, respectively. The bond lengths N1-C9[1.466(7) Å], N1-C18[1.484(8) Å] N2-C10[1.358(8) Å], N2-C11[1.416(9) Å] and C1-F[1.37(8)Å] are within the normal range and comparable to those found in related structures[13,14]. Bond length S1-C20 [1.778(9) Å] S1-C21 [1.81(2) Å] is within the expected range. The plane of the pyrrolidine five membered ring (A) forms a dihedral angle of 85.11° with the plane of indole ring (B), making it almost perpendicular to each other. Pyrrolidine ring (A) [N1\C18\C176C8\C9] is twisted about the N1-C18 bond, with asymmetry parameter ΔC_2=7.85, thereby adopting a *half-chair* conformation. Indole ring is almost planar with maximum deviation for C10 [0.026(6)]. The chain (CH_2-CH_2-S-CH_3) attached to pyrrolidine ring (A) at C18 adopts +*anti-periplanar* conformation with torsion angle C17-C18-C19-C20=177.4(7). Methyl sulfanyl is disordered over two positions [S1/S22, C21/C2A] with site-occupancy ratio of 0.663 and 0.337, respectively.

The structure is stabilized by both intra- [C-H…O] and inter [N-H…O] molecular interaction. In the crystal packing C17-H17…O1 intra molecular hydrogen bond results in a formation of a pseudo- five membered ring generating S(5) graph set motif. Packing of the molecules in the unit cell down the a-axis is shown in the Figure 3. N2-H2A…O3 intermolecular bond connects the molecule to the DMF solvent. The crystal structure is further stabilized by C-H…π interactions, the strongest having the H-centeroid distance of 2.65Å. The geometry of inter- and intra molecular hydrogen bonding in the compound is given in Table 3.

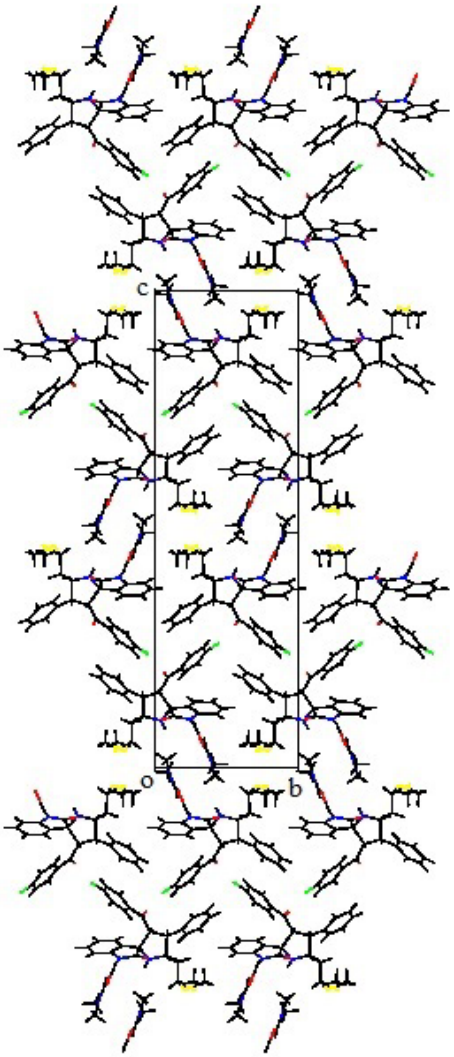


Figure 3. Paking diagram viewed down the a-axis

Table 3. Geometry of inter and intra molecular hydrogen bonds.

D-H…A	D-H	H-A	D-A	D-H…A
N2-H2A…O3	0.86	1.99	2.7529	148
C17-H17…O1^{i}	0.98	2.36	2.8282	109
C3-H3…Cg2^{ii}	0.93	3.06	3.459	107.21
C29-H29C…Cg2^{iii}	0.96	3.3195	4.0778	137.37
C13-H28…Cg5^{iv}	0.93	3.3032	3.8055	116.12
C28-H28…Cg4^{v}	0.93	2.6466	3.5180	156.28

Symmetry parameters: (i) x-1, y+1, z; (ii) x, y, z; (iii) -1/2+x, ½-y, -z; (iv) x, 1+y, z; (v) -1+x, y, z Cg2, Cg4 and Cg5 are the centroid of indole ring[N2\C10\C9\C16\C11], phenyl rings [C11-C16] and [C22-C27] respectively

Conclusion

The compound has been synthesized from multi-component reaction of isatin, methionine and 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one. The molecular and crystal structure is characterized by X-ray diffraction technique with final R-factor of 0.1015. All the rings in the structure are almost planar except the pyrrolidine ring (A) which deviates from planarity and adopts *half-chair* conformation. Hydrogen interactions play significant role in stabilizing the crystal structure and thus crystal structure is stabilized by intra [C-H…O] and inter [N-H…O] molecular interactions. Crystal packing is further influenced by C-H…π interactions.

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