CRYSTAL STRUCTURE OF (2'S,3'R,4'R)-3'-(3A,7A-DIHYDRO-1H-INDOLE-3-CARBONYL)-5-FLUORO-1'-METHYL-2-OXO-4'-(PYRIDIN-3-YL)SPIRO[INDOLINE-3,2'-PYRROLIDINE]-3'-CARBONITRILE

[1]Sivaranjani. T, [2]Raja. R, [3]Hemanathan. K, [1*]Sakthimurugesan. K

[1]Department of Physics, Presidency College, Chennai-05, [2]Department of Physics, Thiruthangal Nadar College, Chennai-51, [3]Department of Physics, Pachaiyappa's college for Men Kanchipuram-6315 02, [1*]Department of Physics, Presidency College, Chennai-05

[1]Department of Physics,
[1]Presidncy College, Chennai-600005

Abstract: The asymmetric unit of the title molecule $C_{27} H_{20} F N_5 O_2$ consists of two molecules differing slightly in conformation and in their intermolecular interactions in the solid. The dihedral angle between the benzene and dioxolane rings is $0.20(7)°$ in one molecule and $0.31(7)°$ in the other. In the crystal, the two molecules are linked into dimmers through pair wise N-H…O hydrogen bonds, with this unit being formed into stacks by two different set of aromatic π-stacking interactions. The stack is connected by C-H…O hydrogen bonds.

Index Terms: single-crystal X-ray study; synthesis; crystal structure; pyrrolidine; fluoro; indoline; C-H…F, C-H…N and N-H…O; hydrogen bonds; π-stacking; T = 295 K; R factor = 0.0519; wR factor = 0.1549; data-to-parameter ratio = 10.5.

I. INTRODUCTION

Spiro-pyrrolidine derivatives are unique tetracyclic 5-HT(2A) receptor antagonists[1]. These derivatives possess anticancer [2] and anti-influenza virus [3] activities. Highly functionalized pyrrolidines have attracted much interest in recent years as they constitute the main structural element of many natural and synthetic pharmacologically active compounds [4]. Optically active pyrrolidines have been used as intermediates, chiral ligands or auxiliaries in controlled asymmetric synthesis [5, 6]. In view of their importance and in continuation of our work on the crystal structure analysis of spiro-pyrrolidine derivatives, we report herein on the synthesis and crystal structure of a new spiro-pyrrolidine derivative. Substituted pyrrolidine compounds possess antimicrobial and antifungal activities against various pathogens [7]. Several optically active pyrrolidine compounds are used as intermediates in controlled asymmetric synthesis [8]. The spiro- indole-pyrrolidine ring system is a frequently encountered structural motif in many biologically important and pharmacologically relevant alkaloids, e.g. vincrinstine, vinblastine and spirotypostatins [9]. Against this background and to ascertain the detailed information on its molecular conformation, the X-ray structure determination of the title compound has been carried out.

II. Experimental

N-Benzylisatin, (1) (0.3 mmol), was mixed with sarcosine, (2) (0.3 mmol), and (E)-2-[(1H-indol-3-yl)carbonyl]-3-(pyridin-3- yl)acrylonitrile in ethanol (10 ml) in a round-bottomed flask. The reaction mixture was heated at 358 K for 3 hours. After cooling to ambient temperature, the reaction mixture was filtered to afford the pure title product as a white solid (yield 92%). The filtrate was left to evaporate slowly and after 48 hours yellow crystals of the title compound were obtained. The solid single product was finally recrystallized from ethanol, giving title compound in good yield as colourless block-like crystals.
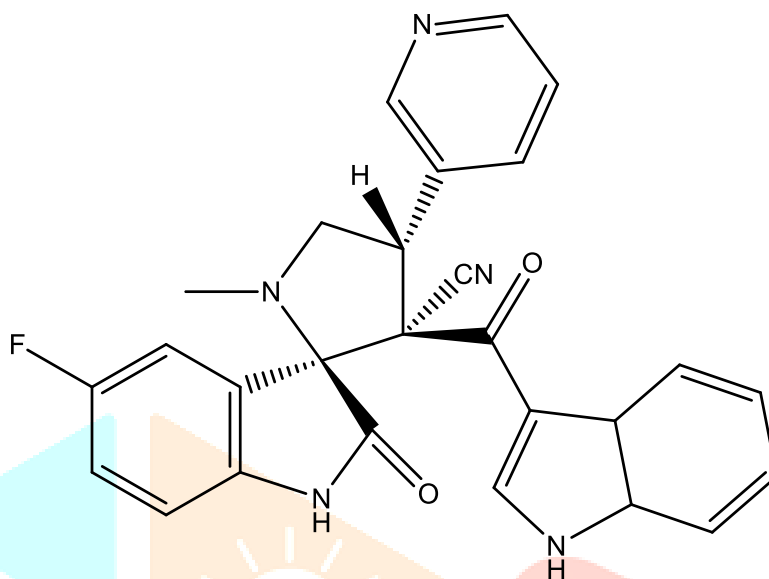

Fig. 1 Scheme

III. Data collection

Data collection: APEX3 (Bruker, 2016)[10]; cell refinement: SAINT (Bruker, 2016); data reduction: SAINT (Bruker, 2016); program(s) used to solve structure: SHELXT (Sheldrick, 2015a)[11]; program(s) used to refine structure: SHELXL2018/3 (Sheldrick, 2015b)[12]; molecular graphics: DIAMOND (Brandenburg & Putz, 2012)[13,14], PLATON (Spek, 2020)[15]; software used to prepare material for publication: SHELXL2018/3 (Sheldrick, 2015b), PLATON (Spek, 2020) and publCIF (Westrip, 2010)[16].

IV. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. H atoms attached to carbon were placed in calculated positions (C—H = 0.95–0.99 Å) while those attached to oxygen were placed in locations derived from a difference map and their coordinates adjusted to give O—H = 0.87Å. All were included as riding contributions with isotropic displacement parameters 1.2–1.5 times those of the attached atoms.

V. Structural Commentary

The asymmetric unit (Fig.2) consists of two independent molecule differ slightly in the orientation of some hydrogen atoms. The indole portion of the molecule containing O1 is planar to within 0.0171(12) Å r.m.s deviation of the fitted atoms= 0.0091 Å) with C7 deviating by 0.017(10) Å from the other indicating a slight twist in the dioxolane ring. The corresponding portion of the second molecule containing O3 is planar to within 0.0041(11) Å (r.m.s deviation of the fitted atoms=0.0031 Å) indicating a conformational difference, albeit small, between the two molecules. The C12-C10-C11-N4 and C39-C34-N9-O4 torsion angles are respectively, 3.9(2)° and -179.96(11)°, indicating the side chain to be nearly coplanar with the benzodioxolane unit. The corresponding torsion angles in the second molecule are virtually the same as above. The indole ring system (C21-C9) is essentially planar with maximum deviations of 0.026(1) Å for atom F1. The mean planes of the thiophene ring systems make dihedral angles of 2.1(2)°, 19.0(1)° and 33.9(1)°, respectively. The N-C [1.477(2) Å] and N-C [1.433(2) Å] bond lengths in the molecules are longer than the mean Nsp^2-Csp^2 bond length value of 1.388(14) Å. The elongation observes may be due to the

electron with drawing character phenylsulfonyl group. The sum of bond angles around N1 [350.2°] indicates the Sp^2 hybridization. The indole moiety is slightly nonplanar as there is dihedral angle of 1.26(14)°.

VI. Superamolecular features

The two molecules are connected into dimmers through N-H…O, N-H…N, C-H…F and C-H…O hydrogen bonds (Table 2 and Fig.3), generating $R_2^2(6)$ loops. In the crystal, the dimmers are connected into stacks extending along the [101] direction through slipped π -stacking interactions between the six membered rings (Fig.4). For the C1-C6 rings, the centroid-centroid distance is 3.6024(11) Å with a slippage of 10185 between molecules at x, y, z and –x,-y+1 –z+1 these paired molecules make week slipped π -stacking interactions with its counter parts in molecules at x-1/2, -y+1/2, z-1/2 and x+1/2,-y+1/2,z+1/2 with centroid-centroid distance of 3.828(11) Å and dihedral angles of 2.41(6)° for both. The slippages for these interactions are 1.572 Å and 1.662 Å, respectively. These differences in the π -stacking interactions also support the independence of the two molecules in the asymmetric unit. The stacks are associated through N1-H1A…O1, C7-H7B…N9, and C6-H6A…O1 hydrogen bonds.
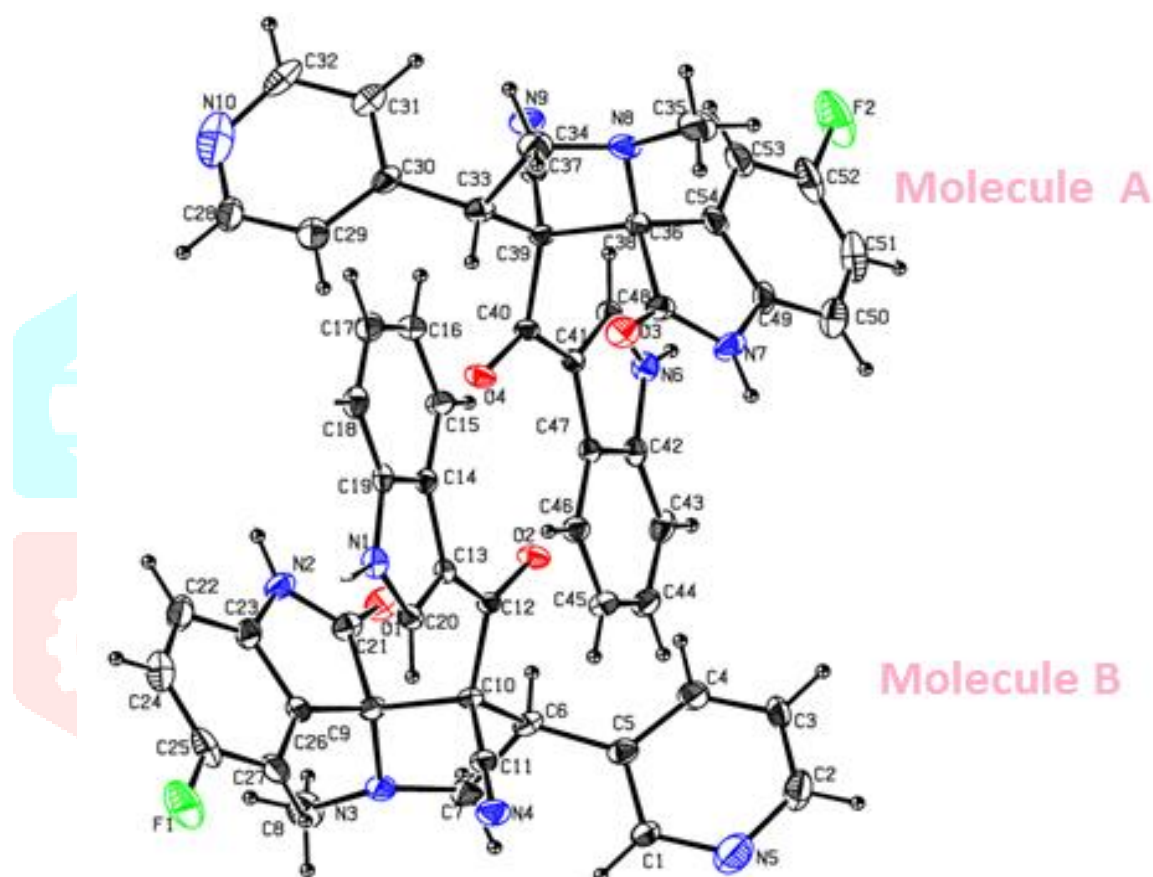

Fig.2. The asymmetric unit with 30% probability ellipsoids.

Fig.3. The asymmetric unit with 50% probability ellipsoids. The N-H…O hydrogen bonds are depicted by dashed lines.
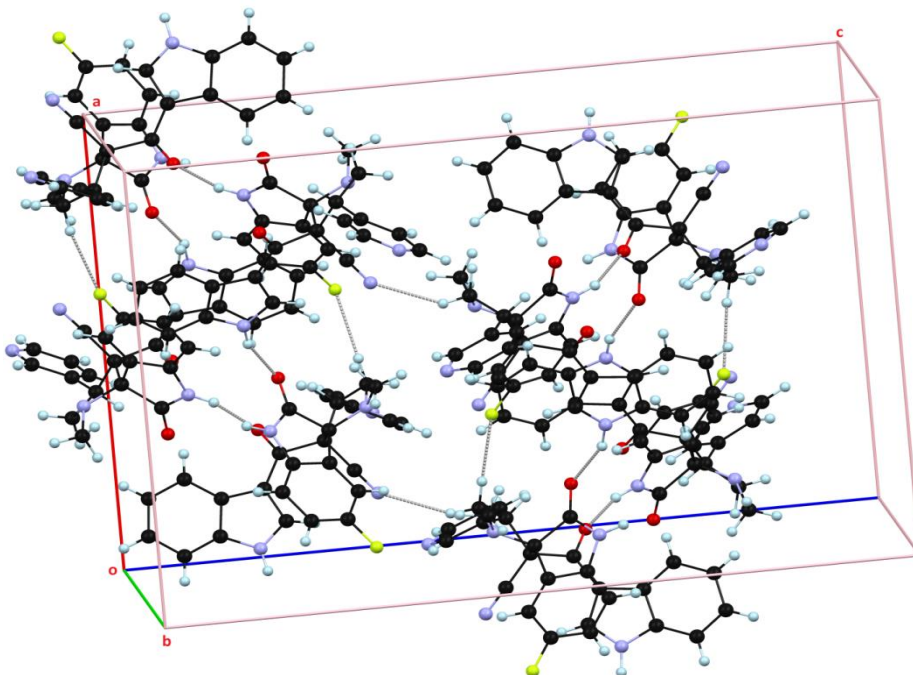

Fig.4 A partial view along a axis of the crystal packing of the title compound. The N-H…O and C-H…F hydrogen bonds are shown as dashed lines (see Table 2 for details).

VII. Table: 1
Crystal Data and Details of the Structure Determination

Parameters	Title of compound
Empirical formula	C27 H20 F N5 O2
Formula weight	465.48
Wavelength	0.71073 Å
Crystal system space group	Orthorhombic Pna21
Unit cell dimensions	a = 16.4758(8)Å
	b = 11.0289(6) Å
	c = 24.904(8) Å
	$\alpha = 90°$
	β 90°
	$\gamma = 90°$
Volume	4525.3(3) Å^3
Z, Calculated density	8, 1.367(1)Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	1936
Crystal size	0.15 x 0.20 x 0.25 mm
θ range	1.6 to 25.5°
Index ranges	$-19 \leq h \leq 19$ $-13 \leq k \leq 13$ $-30 \leq l \leq 30$
Reflections collected / unique	51473 / 8424 [R(int) = 0.046]
Completeness to theta	99.1 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8424/ 0 / 635
Goodness-of-fit on F^2	1.12
Final R indices [I>2sigma(I)]	R1 = 0.0519 wR2 = 0.1549
R indices (all data)	R1 = 0.1083 wR2 = 0.1822
Largest diff. peak and hole	0.30 and -0.30 e.Å^{-3}

VIII. Table 2

Hydrogen-bond geometry (Å , °).

D-H…A	D-H	H…A	D…A	D-H…A
N1-H1A…O1[i]	0.96	1.91	2.805(4)	154.6
N2-H2A…O4[i]	0.88	2.08	2.865(3)	147
N6-H6…O3[ii]	0.86	1.98	2.799(4)	159
N7-H7…O2[ii]	0.86	2.13	2.877(4)	146

Symmetry codes: (i) 1/2+x,1/2-y,z
(ii) -1/2+x,3/2-y,z

IX. ACKNOWLEDGMENT

X. References

[1] Huryn, D. M., Trost, B. M. & Fleming, I. (1991). *Curr. Org. Synth.* **1**, 64–74.

[2] Macrae, C. F., Bruno, I. J., Chisholm, J. A., Edgington, P. R., McCabe, P., Pidcock, E., Rodriguez-Monge, L., Taylor, R., van de Streek, J. & Wood, P. A. (2008). *J. Appl. Cryst.* **41**, 466–470.

[3] Obniska, J., Pawlowski, M., Kolaczkowski, M., Czopek, A., Duszyn'ska, B., Klodzin'ska, A., Tatarczyn'ska, E. & Chojnacka-Wo'jcik, E. (2003). *Pol. J. Pharmacol.* **55**, 553–557.

[4] Peddi, S., Roth, B. L., Glennon, R. A. & Westkaemper, R. B. (2004). *Bioorg. Med. Chem. Lett.* **14**, 2279–2283.

[5] Stylianakis, I., Kolocouris, A., Kolocouris, N., Fytas, G., Foscolos, G. B., Padalko, E., Neyts, J. & De Clercq, E. (2003). *Bioorg. Med. Chem. Lett.* **13**, 1699–1703.

[6] Suzuki, H., Aoyagi, S. & Kibayashi, C. (1994). *Tetrahedron Lett.* **35**, 6119–6122.

[7] Waldmann, H. (1995). *Synlett*, pp. 133–141.

[8] Zapf, C. W., Bloom, J. D., Li, Z., Dushin, R. G., Nittoli, T., Otteng, M., Nikitenko, A., Golas, J. M., Liu, H., Lucas, J., Boschelli, F., Vogan, E., Olland, A., Johnson, M. & Levin, J. I. (2011). *Bioorg. Med. Chem. Lett.* **21**, 4602–4607.

[9] Amalraj, A., Raghunathan, R., Sridevi Kumari, M. R. & Raman, N. (2003). *Bioorg. Med. Chem.* **11**, 407–419.

[10] Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N. L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.

[11] Cordell, G. (1981). *Introduction to Alkaloids: A Biogenic Approach.* New York: Wiley International.

[12] Bruker (2016). *APEX3* and *SAINT*. Bruker AXS Inc., Madison, Wisconsin, USA.

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

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

[15] Spek, A. L. (2020). *Acta Cryst.* E**76**, 1–11.

[16] Westrip, S. P. (2010). *J. Appl. Cryst.* **43**, 920–925.