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Synthesis and fluorine-mediated interactions in methanol-encapsulated solid state self-assembly of an isatin-thiazoline hybrid

Humayun Pervez^a, Maqbool Ahmad^a, Taibi B. Hadda^b, Loic Toupet^c, Muhammad Moazzam Naseer^{d*}

^a Institute of Chemical Sciences, Organic Chemistry Division, Bahauddin Zakariya University, Multan 60800, Pakistan

^b Laboratoire de Chimie des Matériaux (LCM), Faculté des Sciences d'Oujda (FSO), Université Mohammed 1^{er}, 60000-Oujda, Morocco

^c Institut de Physique de Rennes, UMR 625, Université de Rennes 1, Campus de Beaulieu Bat. 11 A, 263 av. Général Leclerc, 35042 Rennes Cedex, France

^d Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan

ABSTRACT: An exciting isatin-thiazoline hybrid molecule **2** having -C=N-N=C- linkage has been synthesized in 88% yield by the reaction of 5-fluoroisatin with *N*-(4-fluorophenyl)hydrazinecarbothioamide followed by condensation of the resultant isatin-thiosemicarbazone intermediate with *p*-chlorophenacyl bromide. The solid state self-assembly of this hybrid molecule was studied by X-ray crystallographic technique. A layered assembly composed of 1D-chains with methanol molecules encapsulated between every two chains is obtained, making a bi-chain sandwich like structure. The supramolecular forces involved in the stabilization of this structure are importantly fluorine-mediated interactions (C-H \cdots F, F \cdots S and F \cdots π) along with others i.e. N-H \cdots O, O-H \cdots O, C-H \cdots O, Cl \cdots π , C-H \cdots π and $\pi\cdots\pi$ interactions. To the best of our knowledge, this is the first example of solid state fluorine-mediated C-H \cdots F, F \cdots S and F \cdots π interactions found in a family of isatin-based compounds.

Keywords: isatin-thiazoline hybrid; synthesis; self-assembly; fluorine-mediated interactions; layered structure

* Corresponding authors. tel.: +92 51 90642129; fax: +92 51 90642241 (M.M.N.).

E-mail addresses: moazzam@qau.edu.pk (M.M. Naseer), pdhpervez@hotmail.com (H. Pervez).

1. Introduction

Weaker hydrogen bonds of the C-H \cdots X-C type play an important role in the stabilization of crystal structures. Hence, the C-H \cdots O, C-H \cdots N, and C-H \cdots Cl hydrogen bonds have increasingly been used in crystal engineering [1-11]. However, the interactions involving “organic fluorine” i.e. C-H \cdots F interactions have always been a controversial subject in contemporary research and their nature still remains obscure [12-17]. According to Pauling’s definition of the hydrogen bond, F atom should be a stronger hydrogen bond acceptor than O and N atoms due to its high electronegativity [18]. But practically, it does not form hydrogen bonds commensurate with electronegativity considerations and has been considered as a very poor acceptor in supramolecular chemistry [14]. Recently, this interaction was evaluated by *ab initio* calculations and found to be much more important in defining the crystal packing than portrayed earlier [19].

In addition to C-H \cdots F interactions, F \cdots X (X=S, π) interactions are the other relatively weak interactions that have recently been recognized in organic fluorinated molecules [20-24]. It is now well-established that drug molecules containing one or more fluorine atoms show superior biological properties as compared to their non-fluorinated analogues perhaps due to better interactions with the receptor sites in our body [25]. Because of its small size, fluorine is also an ideal substituent where change in the electronic properties of the molecules is needed without affecting the steric environment. Furthermore, its lipophilic character also plays an important role in increasing the bioavailability of fluorinated drug molecules [26]. Therefore, more efforts are necessary for appropriate understanding of the intermolecular interactions offered by the fluorine atom.

Isatin (indole-1*H*-2,3-dione) is undoubtedly a privileged scaffold for chemical modification due to its presence in a number of naturally occurring substances [27,28]. Although, a number of its derivatives have been prepared through electrophilic aromatic substitution at positions C-5 and C-7 of the phenyl ring and by *N*-substitution, but the most important and fascinating site for the purpose is C-3 carbonyl group due to its high reactivity with various nucleophiles. It generally undergoes nucleophilic addition or spiroannulation at this position, providing a broad range of 2-oxindole derivatives of immense biological importance [27,28]. Furthermore, isatin is structurally an ideal candidate to serve as a highly variable tecton for the construction of supramolecular assemblies due to its remarkable hydrogen bond donor/acceptor abilities and a relatively large molecular dipole moment [29-31]. Keeping this in view, we very recently reported the synthesis and solid state self-assembly of 5-fluoroisatin-based hybrid molecule **1**, where no intermolecular interactions were observed for fluoro substituent in the presence of N-H \cdots O, C-H \cdots O, C-H \cdots N, C-H \cdots π , $\pi\cdots\pi$, C-H \cdots Cl interactions [32]. This observation and our continuous interest in supramolecular self-assemblies [33-39] increased our curiosity and prompted us to introduce 4-fluoro group as a substitute to 3-methoxy on the central *N*-aryl ring of the rigid core of isatin-thiazoline hybrid **1** to explore the existence of fluorine-mediated interactions in isatin-based compounds. Pleasingly, the approach remained successful and herein, we report the synthesis and methanol-encapsulated layered assembly of isatin-thiazoline hybrid **2** with unprecedented C-H \cdots F, F \cdots S and F \cdots π interactions in a vast library of isatin-based compounds. In addition, this also represents one of the rare examples of fluorine-mediated interactions found in the presence of other strong non-covalent interactions reported so far [40-42].

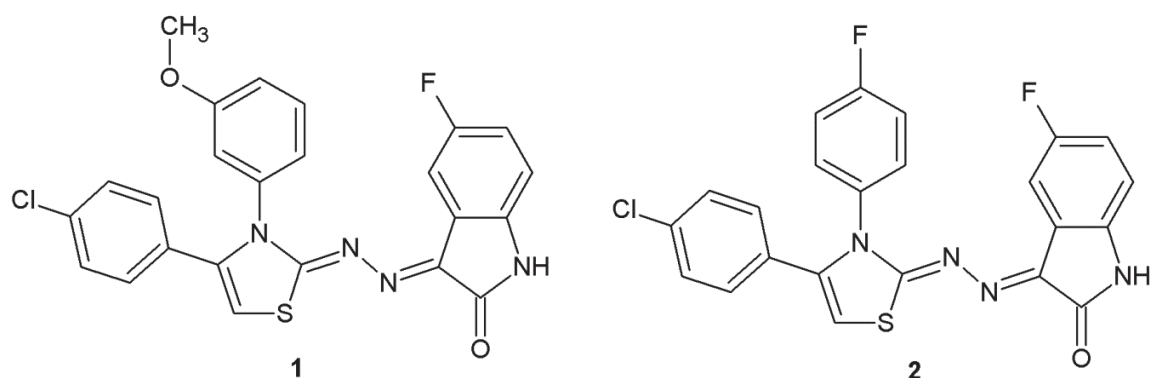


Figure 1. Molecular structures of isatin-thiazoline hybrids **1** and **2**

2. Experimental

2.1 Materials and Methods

All reagents and solvents were used as obtained from the supplier or recrystallized or redistilled as necessary. Thin layer chromatography (TLC) using glass plates coated with Silica gel 60 GF₂₅₄ (E.Marck) was performed to check the progress of the reaction and the purity of the product. The spots were visualized under ultraviolet light at 254 and 366 nm and / or spraying with iodine vapours. Melting point was taken on a Fisher-Johns melting point apparatus and is uncorrected. Elemental analysis was performed on a Leco CHNS-9320 elemental analyzer. Infrared spectrum (KBr disk) was run on Shimadzu 8400. ¹H-NMR spectrum was recorded in C₂D₆SO on Bruker (Rhenistentten-Forchheim, Germany) AM 300 spectrometer operating at 300 MHz, using TMS as an internal standard. ¹H chemical shifts are reported in (ppm) and coupling constants in Hz. Mass spectrum was recorded on agilent 6310 ion trap LC/MS mass spectrometer.

Procedure for the preparation of (3Z)-5-fluoro-1H-indole-2,3-dione 3-[(2Z)-4-(4-chlorophenyl)-3-(4-fluorophenyl)-1,3-thiazol-2(3H)-ylidene]hydrazone (2)

To a solution of 5-fluoroisatin (0.01 mol) in 50% aqueous EtOH (20 mL) containing a catalytic amount of glacial AcOH was added an ethanolic solution (20 mL) of *N*-(4-fluorophenyl)hydrazinecarbothioamide (0.01 mol) with constant stirring. The reaction mixture was then refluxed for 2 h. The solid obtained during refluxing was collected by suction filtration. Thorough washing with hot aqueous EtOH (50%) afforded the desired thiosemicabazone, which was used as such without further purification [43]. The synthesized thiosemicabazone (0.005 mol) was subsequently mixed with *p*-chlorophenacyl bromide (0.005 mol) in absolute EtOH (25 mL) and heated under reflux for 15 h. The refluxate was concentrated on rotary evaporator and the precipitate thus formed was filtered. Thorough washing with *n*-hexane followed by crystallization from water/ethanol furnished the target compound **2** in pure form. The synthesized compound **2** is characterized as follows:

Yield 88% as orange yellow crystals; m.p. 298-300 °C; IR (KBr, cm^{-1}): 3177 (NH stretching), 1705 (C=O), 1624 (C=N); $^1\text{H-NMR}$ (DMSO- d_6 , δ , ppm): 6.75 (dd, $J = 8.7, 4.5$ Hz, 1H, indole C₇-H), 7.03 (td, $J = 9.3, 2.7$ Hz, 1H, indole C₆-H), 7.09 (dd, $J = 9.0, 2.7$ Hz, 1H, indole C₄-H), 7.11 (s, 1H, thiazoline =CH), 7.29 (d, $J = 8.7$ Hz, 2H, phenyl C₂-H, C₆-H), 7.37 (t, $J = 8.7$ Hz, 2H, *N*-phenyl C₂-H, C₆-H), 7.41 (d, $J = 8.7$ Hz, 2H, phenyl C₃-H, C₅-H), 7.55 (dd, $J = 8.7, 4.5$ Hz, 2H, *N*-phenyl C₃-H, C₅-H), 10.50 (s, 1H, indole NH); EIMS (70eV) m/z (%): 468 ($\text{M}^{+} + 2$, 75), 467 ($\text{M}^{+} + 1$, 55), 466 (M^{+} , 100), 440 (8), 439 (9), 438 (18), 437 (11), 305 (6), 304 (8), 303 (12), 292 (35), 291 (19), 290 (82), 288 (22), 234 (7), 232 (16), 170 (8), 168 (19), 153 (26), 149 (13), 136 (9), 134 (7), 133 (6), 121 (12), 108 (6), 95 (14), 75 (7); Anal calcd. for C₂₃H₁₃ClF₂N₄OS: C 59.16, H 2.79, N 12.00; found: C 59.16, H 2.77, N 11.99.

2.2. Crystallographic data collection and structure refinements

Suitable X-ray quality crystals of compound **2** were obtained by slow evaporation of its solution in dichloromethane-methanol solvent mixture at ambient temperature. Single crystal X-ray structural studies of **2** were performed on a CCD Oxford Diffraction XcaliburSaphir 3 diffractometer, employing graphite-monochromated Mo-K α radiation generated from a fine-focus sealed tube ($\lambda = 0.71073\text{\AA}$) at 150(2) K. Data collection strategy was evaluated by using the CrysAlisPro CCD software. Collections of data were observed by the standard ω scan techniques and were scaled and reduced using CrysAlisPro RED software. The structure was solved by direct methods using SIR-97 [44] and refined by least-squares methods on F^2 using SHELXL-97 [45]. The positions of all the atoms were obtained by direct methods. Anisotropic thermal parameters were assigned to all non-hydrogen atoms and the remaining hydrogen atoms were placed in geometrically constrained positions and refined as riding atoms with a common fixed isotropic thermal parameter. The drawing of the complex was realized with PLATON [46]. A summary of the selected crystallographic information is given in Table 1.

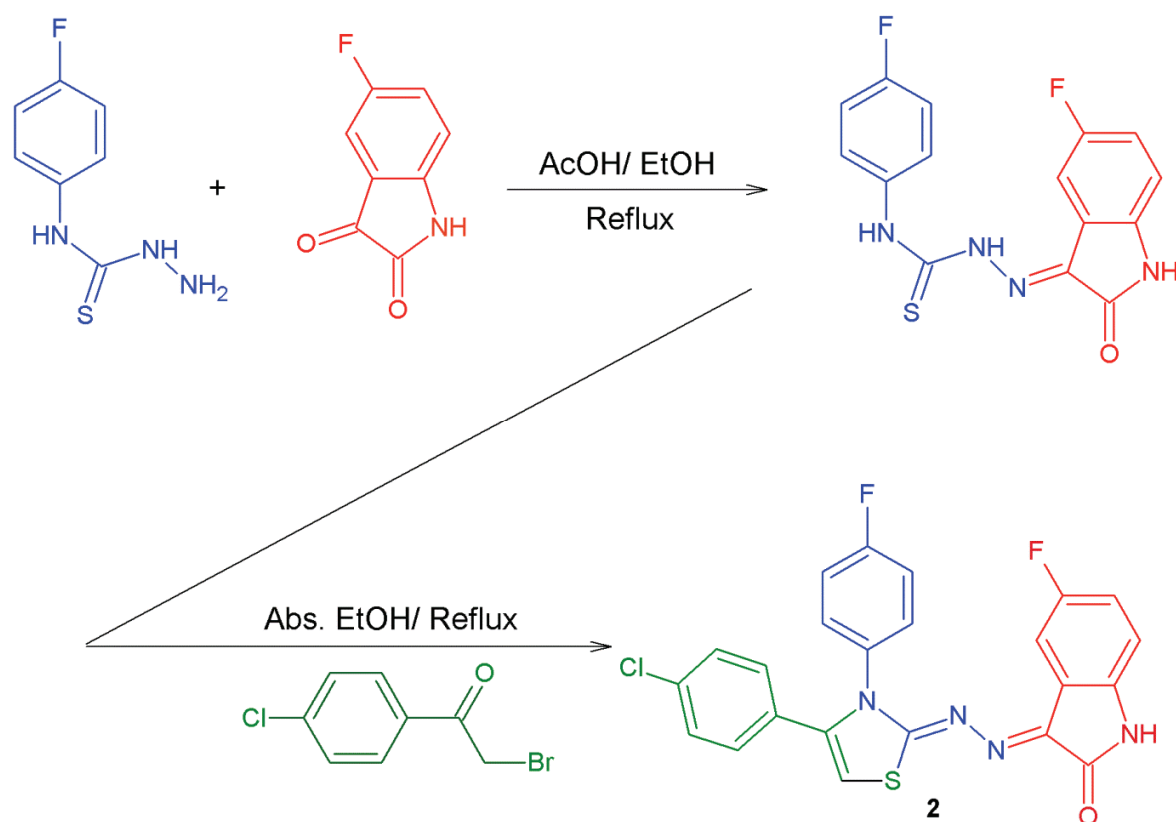
Table 1. Crystal data and structure refinement for **2**

Crystal data	2
CCDC	981215
Chemical formula	C ₂₄ H ₁₇ ClF ₂ N ₄ O ₂ S
M_r	498.93
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	150
a, b, c (\AA)	9.6361 (4), 10.6068 (3), 22.6225 (7)
β ($^\circ$)	97.549 (3)
V (\AA^3)	2292.16 (14)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.30

Crystal size (mm)	0.29 × 0.19 × 0.13
Data collection	
Diffractometer	CCD Sapphire 3 Xcalibur diffractometer
Absorption correction	–
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	19330, 5008, 4183
R_{int}	0.032
$(\sin \theta/\lambda)_{\text{max}}$ (\AA^{-1})	0.639
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.033, 0.086, 1.02
No. of reflections	5008
No. of parameters	308
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e \AA^{-3})	0.30, -0.27

3. Results and discussion

As depicted in Scheme 1, isatin-thiazoline hybrid molecule **2** was synthesized by reacting 5-fluoroisatin with one equivalent of *N*-(4-fluorophenyl)hydrazinecarbothioamide in ethanol solvent containing a catalytic amount of glacial acetic acid in the first step and then treating the resultant product dissolved in absolute ethanol with 4-chlorophenacyl bromide at reflux temperature in the second step.



Scheme 1. Synthesis of isatin-thiazoline hybrid molecule **2**

Single crystals of **2**, suitable for X-ray analysis (Figure 2, Table 1) were cultivated in a dichloromethane/methanol solvent mixture by slow evaporation method and found to have a monoclinic crystal lattice with the $P21/c$ space group. It is important to mention here that these are the same conditions for crystal growth as used previously for compound **1** [32]. In this compound, isatin and the central thiazoline rings that are connected with each other through -C=N-N=C- linkage lie nearly in the same plane. However, the two aryl rings substituted on thiazoline moiety are tilted as compared to the plane of isatin-thiazoline rings. The fluoro-substituted aryl ring present at N4-of the thiazoline moiety is positioned in such a way that H5 of the isatin is located on almost top and the centre of its aromatic ring plane with a distance of 2.977 Å. The dihedral angle between the plane of fluoro-substituted aryl and thiazoline rings is

69.67° (C9-N4-C18-C19). The chloro-substituted aryl ring at C-10 of the thiazoline ring is less tilted as compared to the N4-aryl one with a dihedral angle of 42.06° (N4-C10-C12-C17) from the isatin-thiazoline plane. In the thiazoline ring, the S(1)-C(9) and S(1)-C(11) bond lengths are 1.733(14) Å and 1.735(15) Å, respectively, with the C(9)-S(1)-C(11) bond angle being 90.10(7)°. Other selected bond lengths and bond angles are presented in the caption to figure 2.

The most significant and interesting feature of this compound is its molecular packing in the solid state, stabilized by fluorine-mediated interactions (C-H...F, F...S and F... π) (Figure 3) in addition to other non-covalent interactions (N-H...O, O-H...O, C-H...O, Cl... π , C-H... π , π ... π) (Table 2). The crystal structure revealed methanol-encapsulated layered assembly, composed of 1D-supramolecular chains (Figure 4). As shown in figures 4a & 4b, methanol molecules are sandwiched between every two chains of a layer. Each 1D-chain of this assembly is formed by the lateral arrangement of molecules by means of F...S [F(1)...S(1) 3.014 Å] and F... π [F(1)...C(11) 3.123 Å] interactions. The molecules in every chain of a layer with respect to another are inverted. Two neighbouring chains, which are encapsulating the methanol molecules by means of mainly N-H...O [N(1)-H(1)...O(2) 1.981 Å], O-H...O [O(2)-H(2A)...O(1) 1.871 Å] and C-H...O [C(3)-H(3)...O(2) 2.521 Å] interactions, are connected with each other through C-H...O [C(2)-H(2)...O(1) 2.448 Å] interactions. The two consecutive chains, which are sandwiching the methanol molecules (a bi-chain sandwich) are connected to the next bi-chain sandwich with the help of Cl... π [Cl(1)...C(20) 3.406 Å, Cl(1)...C(21) 3.261 Å] interactions. Furthermore, each layer of this assembly is connected to the next layer by means of C-H...F [C(22)-H(22)...F(1) 2.597 Å], C-H... π [C(24)-H(24)...C(15) 2.876 Å, C(20)-H(20)...C(3) 2.828 Å], C-H...O [C(17)-H(17)...O(1) 2.601 Å] and π ... π [C(9)...N(2) 3.232 Å] interactions between anti-parallel stacked molecules of **2**, providing an overall multi-layered structure (Figure 4c).

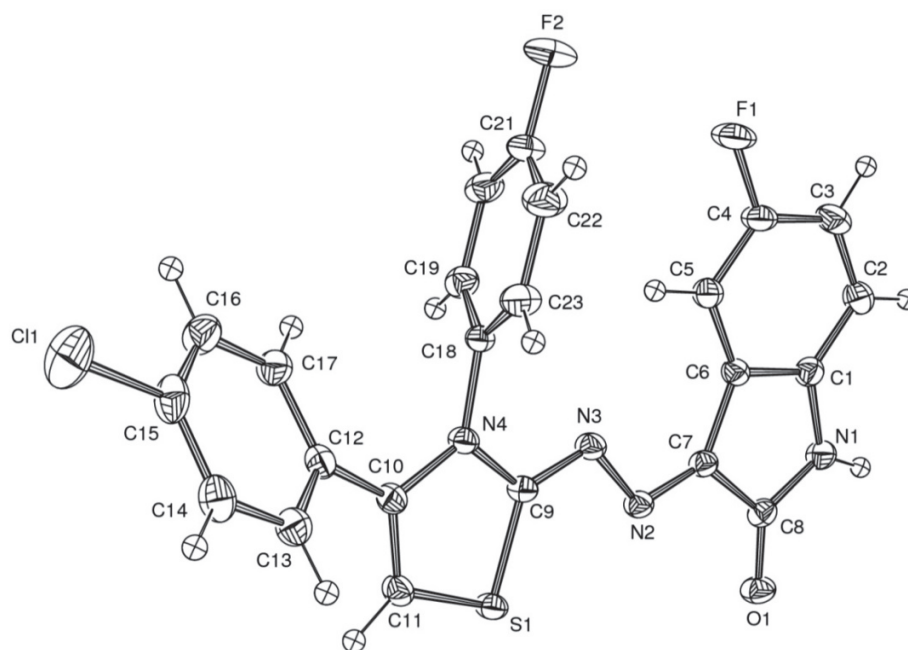


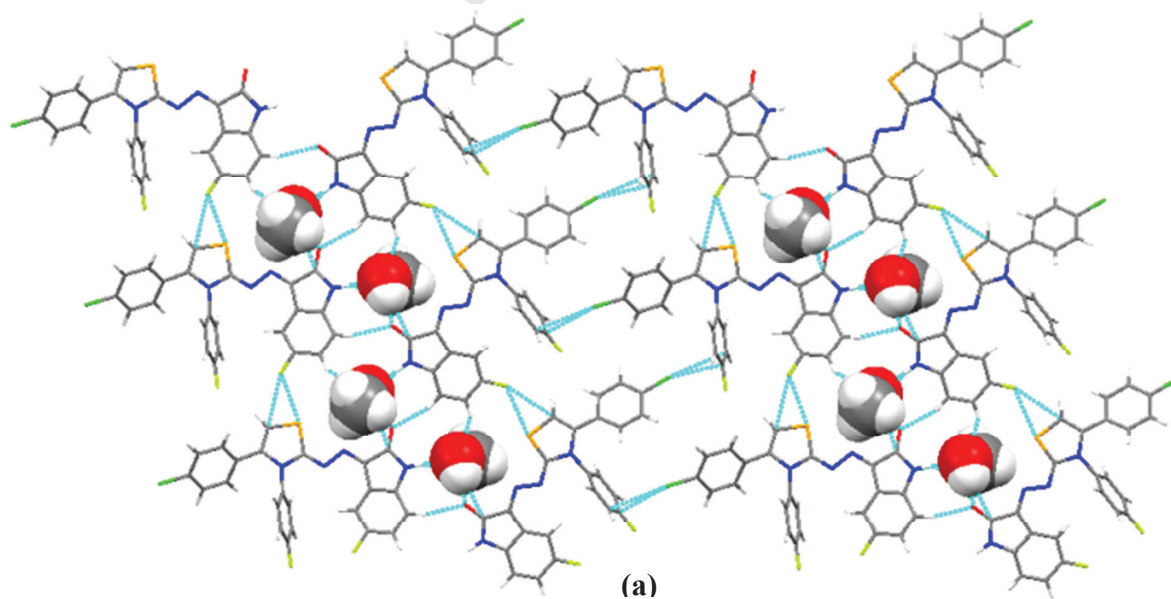
Figure 2. X-ray crystal structure of **2**. Selected bond lengths (Å): Cl(1)-C(15) 1.373(16); S(1)-C(9) 1.733(14); S(1)-C(11) 1.735(15); F(1)-C(4) 1.368(17); F(2)-C(21) 1.360(18); O(1)-C(8) 1.230(18); N(1)-C(8) 1.356(19); N(1)-C(1) 1.405(19); N(1)-H(1) 0.8800; N(2)-C(7) 1.298(19); N(2)-N(3) 1.363(16); N(3)-C(9) 1.309(18); N(4)-C(9) 1.369(18); N(4)-C(10) 1.406(18); N(4)-C(18) 1.443(17). Selected bond angles (°): C(9)-S(1)-C(11) 90.10(7); C(8)-N(1)-C(1) 111.25(12); C(7)-N(2)-N(3) 111.95(12); C(9)-N(3)-N(2) 111.84(12); C(9)-N(4)-C(10) 113.78(11); C(9)-N(4)-C(18) 118.44(11); C(10)-N(4)-C(18) 127.76(11).



Figure 3. Crystal packing of **2** highlighting fluorine-mediated C-H \cdots F, F \cdots S and F \cdots π interactions

Table 2. Non-covalent interactions stabilizing the methanol-encapsulated solid state self-assembly of compound **2**

Interaction type	Atoms involved	Distance (Å)
C-H \cdots F	C(22)-H(22) \cdots F(1)	2.597
F \cdots S	C(4)-F(1) \cdots S(1)	3.014
F \cdots π	C(4)-F(1) \cdots C(11)	3.123
N-H \cdots O	N(1)-H(1) \cdots O(2)	1.981
O-H \cdots O	O(2)-H(2A) \cdots O(1)	1.871
C-H \cdots O	C(3)-H(3) \cdots O(2)	2.521
	C(2)-H(2) \cdots O(1)	2.448
	C(17)-H(17) \cdots O(1)	2.601
C-H \cdots π	C(24)-H(24) \cdots C(15)	2.876
	C(20)-H(20) \cdots C(3)	2.828
Cl \cdots π	Cl(1) \cdots C(20)	3.406
	Cl(1) \cdots C(21)	3.261
π \cdots π	C(9) \cdots N(2)	3.232



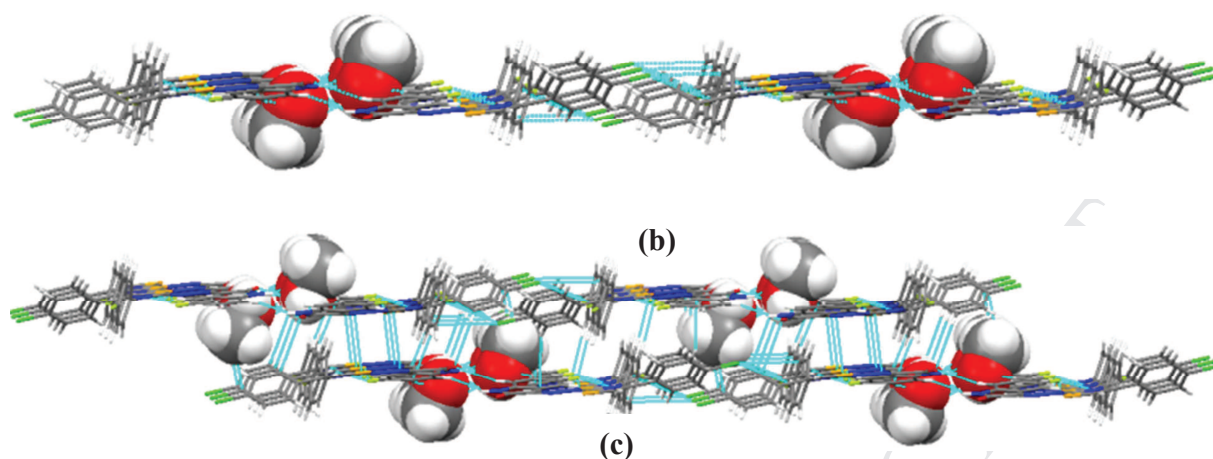


Figure 4. Crystal packing of compound **2**: a) view of four neighbouring 1D-chains having methanol molecules encapsulated between two chains forming a bi-chain methanol sandwich along *a*-axis; b) view of a layer along *b*-axis; c) view of two consecutive layers along *b*-axis

To the best of our knowledge, fluorine-mediated C-H \cdots F, F \cdots S and F \cdots π interactions described here have not been reported so far in a family of isatin-based compounds. It is worth mentioning that C-H \cdots O interactions observed in **1** due to the presence of methoxy substituent are outweighed by the fluorine-mediated interactions found in the present case [32]. The introduction of fluoro substituent as a substitute to methoxy on the central aryl ring of **2** led to the appearance of fluorine-mediated interactions. The strategy to observe fluorine-mediated interactions used here could possibly be used in other rigid systems to explore and understand their positive effects on the biological properties of a specific drug molecule, in addition to their applications in crystal engineering field [47].

4. Conclusions

In summary, we have synthesized an interesting isatin-thiazoline hybrid molecule **2** and studied its solid state self-assembling behaviour by X-ray crystallography. A multi-layered methanol encapsulated network assembly, which is composed of various 1D-chains, has been observed. Fascinatingly, methanol molecules are sandwiched between two 1D-chains of this assembly. The

notable supramolecular interactions involved in the stabilization of this assembly are C-H \cdots F, F \cdots S and F \cdots π , which were not only absent in our previously reported isatin-thiazoline hybrid **1** but also, to the best of our knowledge, never reported earlier in the family of isatin-based compounds by other workers. As illustrated in the present example and also revealed from our previous study and the literature survey, fluorine-mediated interactions may occur even in the presence of other strong non-covalent interactions but it depends largely on the geometry of the molecules. Furthermore, they are not very weak interactions (C-H \cdots F = 2.597 Å) and may have significant ability to direct the molecular packing, which highlights their much larger role in the crystal packing than anticipated so far [47]. The general perception that organic fluorine hardly ever accepts hydrogen bond [14] has been found to gradually change during the past two decades and its structure directing role is now recognized [16]. However, to understand its role in biology and use as a reliable synthon in crystal engineering still needs more research.

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Research Highlights:

- An isatin-thiazoline hybrid molecule having -C=N-N=C- linkage has been synthesized.
- Solid state self-assembly was studied by X-ray crystallographic technique.
- A bi-chain sandwich like structure with methanol molecules encapsulated between every two chains is obtained.
- Fluorine-mediated interactions are involved in the stabilization of this assembly.

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

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No syntax errors found. CIF dictionary Interpreting this report

Datablock: shelx

Bond precision:	C-C = 0.0021 A	Wavelength=0.71073	
Cell:	a=9.6361 (4)	b=10.6068 (3)	c=22.6225 (7)
	alpha=90	beta=97.549 (3)	gamma=90
Temperature:	150 K		
	Calculated	Reported	
Volume	2292.17 (14)	2292.16 (14)	
Space group	P 21/c	P 21/c	
Hall group	-P 2ybc	-P 2ybc	
Moiety formula	C23 H13 Cl F2 N4 O S, C H4 ?		
	O		
Sum formula	C24 H17 Cl F2 N4 O2 S	C24 H17 Cl F2 N4 O2 S	
Mr	498.93	498.92	
Dx, g cm-3	1.446	1.446	
Z	4	4	
Mu (mm-1)	0.304	0.304	
F000	1024.0	1024.0	
F000'	1025.55		
h,k,lmax	12,13,28	12,13,28	
Nref	5012	5008	
Tmin,Tmax	0.933,0.961		
Tmin'	0.917		
Correction method=	Not given		
Data completeness=	0.999	Theta(max)=	26.997
R(reflections)=	0.0333 (4183)	wR2(reflections)=	0.0864 (5008)
S =	1.022	Npar=	307

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

Alert level C

PLAT790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd. # 1 Note
C23 H13 Cl F2 N4 O S

Alert level G

PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms 2 Report
PLAT169_ALERT_4_G The CIF-Embedded .res File Contains AFIX 1 Recds 2 Report
PLAT790_ALERT_4_G Centre of Gravity not Within Unit Cell: Resd. # 2 Note
C H4 O

0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
1 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
3 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
0 ALERT type 2 Indicator that the structure model may be wrong or deficient
0 ALERT type 3 Indicator that the structure quality may be low
3 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

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Datablock shelx - ellipsoid plot

