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A comprehensive understanding of the synthons involving C–H···F–C hydrogen bond(s) from structural and computational analyses

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Abstract:

The studies of weak interactions involving "organic fluorine" have resulted into a number of conflicts in the literature. Although the involvement of a C–F group in influencing the crystal packing has been demonstrated among various compounds, none have emphasized the consistency of the synthons formed by C–H···F–C hydrogen bonds. Herein, we have attempted to draw a correlation between the formations of a particular synthon with the position of the fluorine substitutions in the current structural analyses of a model system of tetrafluoro substituted *N*-benzylideneanilines. Few frequently occurring supramolecular synthons involving C–H···F–C hydrogen bonds have been identified in these and related molecules and have been quantified by *ab-initio* calculations using MP2 level of theory at 6-31+G* basis set in the gas phase. The topological properties of these C–H···F–C hydrogen bonds have been calculated using AIM2000. The nature, strength, directionality and the synthons reproducibility of C–H···F–C hydrogen bonds are the key features presented in this article.

Introduction:

The non-covalent interactions utilized by the molecules to communicate with their neighbors need to be understood to control and manipulate them to design and build a desired supramolecular architecture for specific applications. Designing of supramolecular structures utilizing the possible intermolecular non-covalent interactions has wide applications in the fields of molecular recognition,[1] host-guest chemistry,[2] supramolecular chemistry[3] *etc*. When the conversation between the molecules is loud enough, then it becomes easier to understand them, but when their conversation is feeble, it becomes a challenging task to understand them. This is actually the case for strong hydrogen bonds, which are very well understood and explored significantly in the literature,[4a,b] the weaker interactions are yet to be fully understood and utilized appropriately in designing desired materials.[4c] The weak hydrogen bonds like C–H···O, C–H···N *etc*. have been understood in great detail in the literature,[4c] while the same involving halogens have remained a controversial area in crystal engineering. Fluorine, the most electronegative element, is expected to form strong hydrogen bonds, as it does in HF, but in different environment it has been shown to be reluctant to form strong hydrogen bonds.[5] Although the replacement of a C–H bond by a C–F bond does not bring significant change in the size of the molecule, but due to high electronegativity and low polarizability of fluorine result into a considerable change in the electronic properties of the concerned molecule.[6] While, Shimoni and Glusker pointed out that although C–F acceptor is not able to compete with C–O and C–N acceptors, the influence of the C–F group should not be ignored in predicting the modes of crystal packing,[7] Howard *et al.,*[8] based on the limited number of structures available in CSD and computational studies had claimed that "true hydrogen bonds to fluorine are extremely rare". Dunitz also commented on the poor acceptor capabilities of organic fluorine.[5] Thalladi *et al*., through an extensive study on C–H···F–C interactions in fluorobenzenes have highlighted the importance of them in crystal engineering.[9] Dunitz once again questioned the importance of such interactions by stating that one of the hypothetical high pressure structures of benzene had C–H···H interactions with the same structure-directing ability and influence on the intermolecular interaction energy as the intermolecular C–H···F–C interactions in fluorobenzene.[10] Thakur *et al*. have shown that C–H···H–C interactions in the high pressure structure of benzene are not due to close packing, rather those interactions should be represented as $H^{\delta+}\cdots H^{\delta-}$ and in this way with respect to hydrogen bonds, this structure also follows the similar trend of packing as that of fluorobenzenes.[11] Thus, the topic of weak C–H···F–C hydrogen bonds has always been controversial, and therefore interesting.

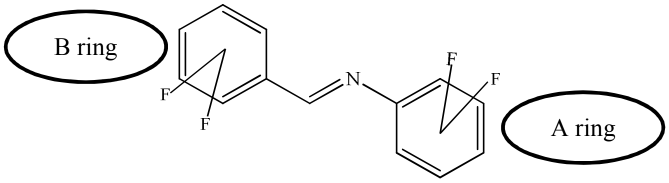
A number of systematic studies have been reported in the recent literature on various model systems to achieve a detail understanding and to gain considerable insight into the nature, strength and directionality of C–H···F–C hydrogen bonds in the absence[12-15] as well as in the presence[16-20] of strong hydrogen bond donor and acceptor sites. Recent structural studies on fluorine substituted indole derivatives,[21] isoquinolines,[22] *N*-benzylideneanilines,[23] aromatic azo compounds[24] *etc*. have established the role of organic fluorine in guiding the crystal packing in different types of molecular framework, although frequently occurring synthons involving only C–H···F–C hydrogen bond(s) have not been analyzed systematically till date.

Therefore, we have attempted to understand the strength, directionality and structure controlling ability of the C–H···F–C mediated supramolecular synthons in the current structural study of tetra-fluorinated *N*-benzylideneanilines, which do not have any site for the formation of strong hydrogen bonds. Recently, we have analyzed the formation of various synthons involved in the crystal packing of difluoro substituted *N*-benzylideneanilines,[23] and afterwards we have analyzed the effect of replacement of one of the fluorine atoms by Cl or Br in the same system.[25] In those cases, we observed that the synthon formed *via* C–H···F–C hydrogen bond remained unaltered when the non-interacting F was replaced by Cl or Br, whereas the replacement of interacting fluorine with Cl or Br led to the formation of completely different packing motifs. The structural analyses on halogenated azobenzens have highlighted that organic fluorine prefers C–H···F–C hydrogen bonds, while the heavier halogens (Cl and Br) prefer C–X···X–C (X = Cl, Br) interactions in the solid state.[24] In this article, we are highlighting the effect of incorporation of more fluorine atoms in the studied molecular framework on their crystal packing. In addition, we intend to emphasize the strength, directionality and frequent appearance of few synthons formed through C–H···F–C hydrogen bonds.

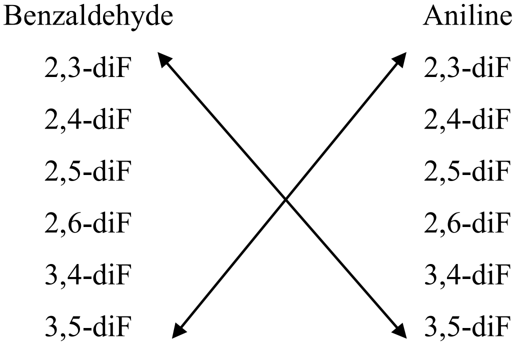
Experimental:

Procedure for the synthesis of all the compounds is given in the ESI. Scheme 1 describes all the synthesized molecules. There are six different difluoro substituted aldehydes and anilines, namely 2,3; 2,4; 2,5; 2,6; 3,4; 3,5. So, a total of 36 (6×6) compounds were synthesized by using various combinations of difluorobenzaldehydes and difluoroanilines as can be inferred from the following scheme 2. The compound identification numbers in this manuscript are in continuation with our earlier reports.[23,25] Out of 36 synthesized compounds, 35 compounds were found to be solid at room temperature (25 ^{o}C) while one compound was found to exist as liquid (**85**).

Scheme 1: Tetrafluoro substituted *N*-benzylideneanilines



Scheme 2: Possible combination of different difluoro substituted benzaldehydes and anilines, which were condensed together to give the required product.



Benzaldehyde	Aniline
2,3-diF	2,3-diF
2,4-diF	2,4-diF
2,5-diF	2,5-diF
2,6-diF	2,6-diF
3,4-diF	3,4-diF
3,5-diF	3,5-diF

Compound identification table

C.N. (Compound Number)	Position of F atoms on benzaldehyde ring (B)	Position of F atoms on aniline ring (A)
52	3,4	2,3
53	3,4	2,4
54	3,4	2,5
55	3,4	2,6
56	3,4	3,4
57	3,4	3,5
58	3,5	2,3
59	3,5	2,4
60	3,5	2,5
61	3,5	2,6
62	3,5	3,4
63	3,5	3,5
64	2,3	2,3
65	2,3	2,4
66	2,3	2,5
67	2,3	2,6
68	2,3	3,4
69	2,3	3,5

C.N. (Compound Number)	Position of F atoms on benzaldehyde ring (B)	Position of F atoms on aniline ring (A)
70	2,4	2,3
71	2,4	2,4
72	2,4	2,5
73	2,4	2,6
74	2,4	3,4
75	2,4	3,5
76	2,5	2,3
77	2,5	2,4
78	2,5	2,5
79	2,5	2,6
80	2,5	3,4
81	2,5	3,5
82	2,6	2,3
83	2,6	2,4
84	2,6	2,5
85	2,6	2,6
86	2,6	3,4
87	2,6	3,5

All the synthesized compounds were characterized by ^{1}H NMR spectroscopy (400 MHz, Bruker Biospin Advance-III NMR spectrometer) (ESI, figures S1: 1 to 36) and

FTIR spectroscopy (Bruker Tensor 72, equipped with diamond cell ATR) (ESI, figures S2: 1 to 36]. Powder X-ray Diffraction (PXRD) data were recorded on a Rigaku Ultima IV diffractometer using parallel beam geometry, Cu – K_α radiation, 2.5° primary and secondary solar slits, 0.5° divergence slit with 10 mm height limit slit, sample rotation stage (120 rpm) attachment and DTex Ultra detector. The tube voltage and current applied were 40 kV and 40 mA respectively. The data sets were collected over 2θ ranging from 5 to 50° with a scanning speed of 5° per minute with 0.02° step for all the solid compounds.

The PXRD patterns have been simulated from the crystal coordinates using Mercury 3.3[26] and have been compared with the observed PXRD patterns (using WINPLOTR[27]) (ESI, figures S3: 1 to 35). Melting points (table S1) were determined from the DSC data (Perkin Elmer DSC 8000) (ESI, figures S4: 1 to 36). The ORTEP figures of all the compounds have been drawn at 50% probability for the non-H atoms using Mercury 3.3 and are shown with the atom labels. (ESI, figures S5: 1 to 30).

Diffraction Data Collection and Structure Solution:

Single crystals of all the purified solids were grown from different solvents and solvent mixtures (Table 1) at low temperature. Single crystal X-ray diffraction data collection for all the compounds were done using a Bruker AXS KAPPA APEX-II CCD diffractometer (Monochromatic Mo – K_α radiation) equipped with Oxford cryosystem 700Plus at 100.0 (1) K. Data collection and unit cell refinement for the data sets were performed with Bruker APEX-II[28] suite. Data reductions were done using SAINT V7.685A12 (Bruker AXS, 2009) and SADABS V2008/112 (Bruker AXS) were used for the scaling and absorption correction. Structure solutions have been done using Olex2[29] or WinGx[30] packages using SHELXS97[31] and the structures were refined using SHELXL97. All the hydrogen atoms were geometrically fixed and refined using the riding model. Table S1a (ESI) lists the crystal and refinement data for all the compounds. All the packing and interaction diagrams have been generated using Mercury 3.3. PARST[32] and PLATON[33] programs have been used for the geometric calculations.

Theoretical Calculations:

Due to the absence of any strong hydrogen bonding sites in our studied compounds, the types of interactions that could be present in our system are C–H···π, π···π, C–H···F–C, C–F···F–C, C–F···π. Out of these our main interest is to study the strength and directionality of the synthons formed by the utilization of C–H···F–C hydrogen bonds. Therefore, the stabilization energies of the molecular dimers formed through C–H···F–C hydrogen bonds have been calculated at MP2[34] level of theory at 6-31+G(d) basis set using Gaussian09[35] as described in detail in our earlier publication.[25] The stabilization energies ($SE_{G09} = E_{dimer} - 2\times E_{monomer}$) of these dimers were corrected for the basis set superposition error (BSSE) by the counterpoise method.[36] Gauss view[37] was used to prepare input files for Gaussian09 and also to visualize the molecules during the calculations. The discussion related to the much weaker and hence almost insignificant C–H···π and π···π interactions in these molecules have been placed in the ESI.

Analysis of topological properties:

To characterise the topological properties of the C–H···F–C hydrogen bonds, Atoms In Molecules (AIM) theory of Bader with the AIM2000 program was used.[38] In all the studied dimers, a (3, -1) bond critical point (BCP) has been found between the interacting H and F atoms. The topological properties of all C–H···F hydrogen bonds have been calculated at the BCPs. The electron density (ρ), Laplacian ($\nabla^2\rho$), local potential ($V(\mathbf{r}_{CP})$), kinetic ($G(\mathbf{r}_{CP})$) and total energy densities ($E(\mathbf{r}_{CP})$), which were found at BCPs have been plotted against bond path (R_{ij}) using sigma plot.[39]

Results and Discussion:

Out of 36 synthesized compounds with tetrafluoro substituents, crystals of 30 compounds could be grown and the structures of these 30 compounds were determined. The detailed structural descriptions of these compounds are given in the ESI. We intend to carry forward the results of our earlier publications, where we had described some synthons found to remain unaltered upon replacement of non-interacting F with Cl or Br.[25] In the following sections we discuss the structural features defined by those synthons upon the addition of more fluorine atoms to the molecule.

Synthon I (A, B and C): The following synthons **I(A), I(B) and I(C)** involving the imine hydrogen occur frequently in the studied compounds (figure 1). Out of these, the synthon I(A) forms a molecular chain, which can be presented through Etter's graph set notation[40] as C(6), while the other two form a ring involving two C–H donors and one C–F acceptor and therefore, can be identified as $R_2^1(7)$ In our earlier report we mentioned that "Further in the cases of **3**, **18**, **36**, **6**, **21** and **39**, where F is present in the *ortho-* position on the A ring and F/Cl/Br is present at *para-* or *meta-* position on the B ring, the structures of those compounds have been majorly influenced by the intermolecular C–H···F–C hydrogen bond (with stabilization energy in the range of 4-5 kcal/mol) involving the imine hydrogen and the *o*-F of the A ring". The same has been noticed here as well. When the position of the fluorine atom on the B ring are either 3,4 or 3,5 and one of the fluorines present on A ring is at *ortho*-position then this type of synthons are always observed. In these particular synthons, the adjacent H present at the A or B ring may also participate in C–H···F–C hydrogen bond formation depending upon the orientation of the acceptor molecule with respect to the donor molecule. It is noteworthy that the C–H···F–C hydrogen bonds involving imine H have always been observed to be short (mostly between 2.3-2.5 Å) and directional and the neighboring hydrogen bonds are formed in a co-operative manner.

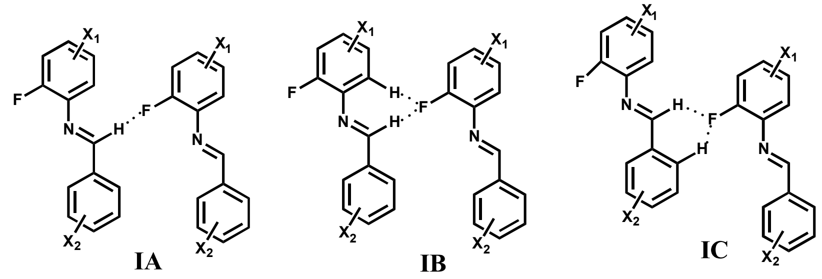
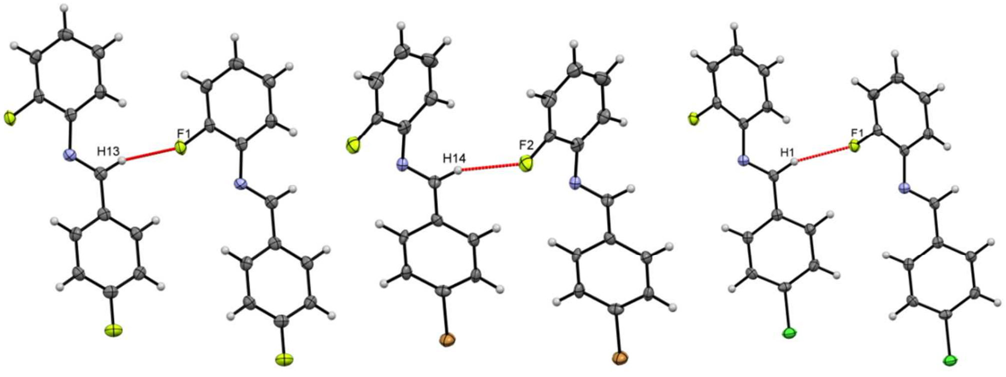


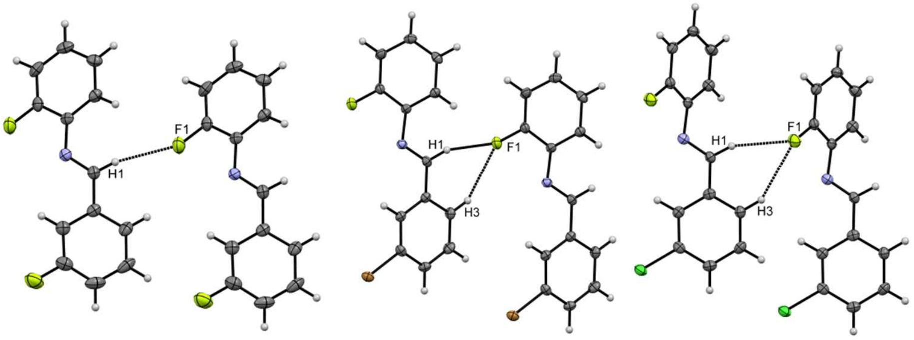
Figure 1: A schematic representation of the synthons I(A) [C(6)], I(B) [$R_2^1(7)$] and I(C) [$R_2^1(7)$]

Occurrence of synthon I(A)/I(C) in dihalogen substituted *N*-benzylideneanilines:

When we had a F atom at the *ortho* position of A ring and 2nd F/Cl/Br was present at the *para* or *meta* position of B ring (C.N.- **3**, **18**, **36**, **6**, **21** and **39,** reported in the reference no. 23 and 25), the following dimers (which are actually the building blocks of the C(6) chain) connected by short and directional C–H···F–C hydrogen bonds (with stabilization energy in the range of 4-5 kcal/mol) were observed in the crystal structures of the respective compounds (figure 2, table 1).



CN **3**: **4F(B)-2F(A)** CN **18**: **4Br(B)-2F(A)** CN **36**: **4Cl(B)-2F(A)**

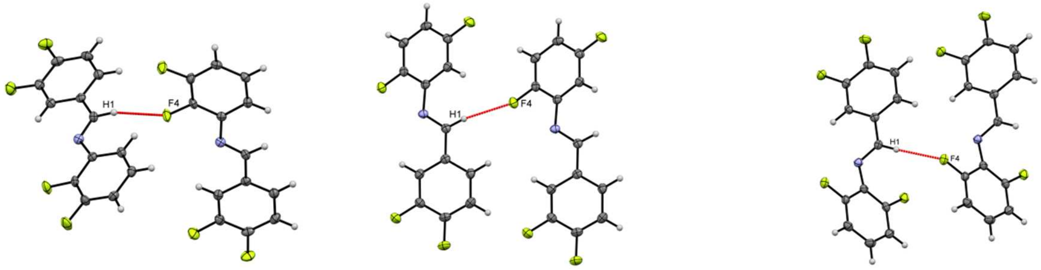


CN **6: 4F(B)-2F(A)** CN **21: 4Br(B)-2F(A)** CN **39: 4Cl(B)-2F(A)**

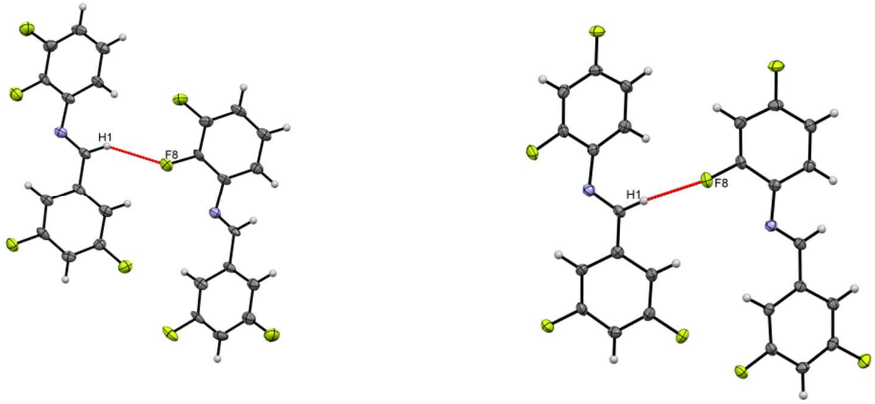
Figure 2: Formation of synthon I(A) and I(C) in the cases of compound **3**, **18, 36, 6**, **21** and **39**.

Occurrence of synthon I(A)/I(B) in tetrafluoro substituted *N*-benzylideneanilines:

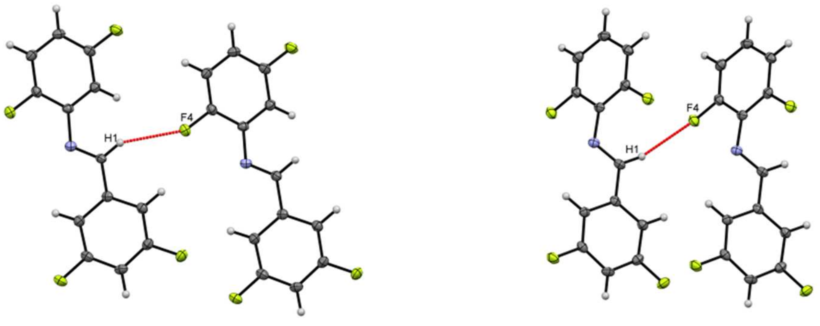
In the cases of compounds **52**, **53**, **54** and **55**, when one of the F in the A ring is present at the *ortho* position and the position of the fluorine atoms on the B ring is either 3,4 or 3,5; synthon I(A) has been observed (figure 3, table 1) except in the case of CN **53**: **3,4-diF(B)–2,4-diF(A).**



CN **52**: **3,4-diF(B)–2,3-diF(A)** CN **54**: **3,4-diF(B)–2,5-diF(A)** CN **55**: **3,4-diF(B)–2,6-diF(A)**



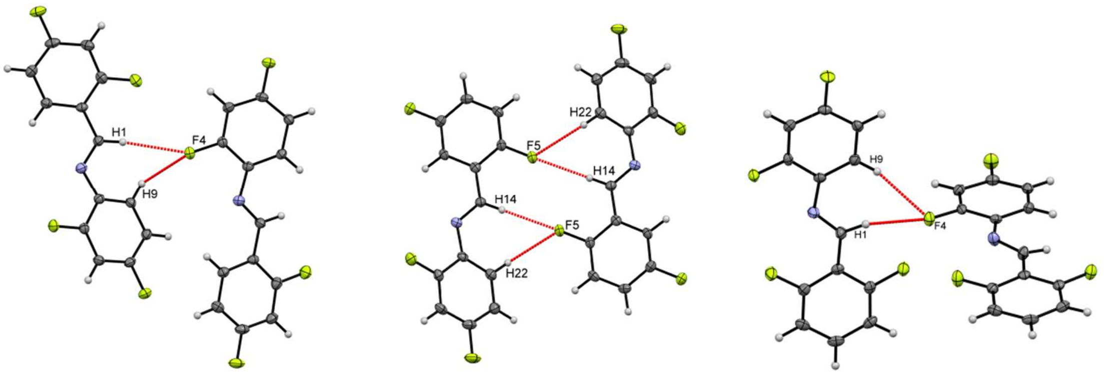
CN **58**: **3,5-diF(B)–2,3-diF(A)** CN **59**: **3,5-diF(B)–2,4-diF(A)**



CN **60**: **3,5-diF(B)–2,5-diF(A)** CN **61**: **3,5-diF(B)–2,6-diF(A)**

Figure 3: formation of synthon I(A) in the compounds **52**, **54**, **55**, **58**, **59**, **60** and **61.**

Synthon I(B) has been identified in the cases of compounds **71**, **77** and **83**, where F atoms of the A ring are present at the 2,4 positions and the positions of fluorine atoms on the B ring are 2,4; 2,5 and 2,6 (figure 4, table 1).



CN **71**: **2,4-diF(B)–2,4-diF(A)** CN **77**: **2,5-diF(B)–2,4-diF(A)** CN **83**: **2,6-diF(B)–2,4-diF(A)**

Figure 4: Formation of synthon I(B) in the compounds **71**, **77**, and **83.**

Table 1: Details of the geometrical parameters for all C–H···F–C hydrogen bonds, the values of electron densities and Laplacians at their BCPs.

Code	C–H···F	*d* (H···F/Å)	θ (∠C–H···F/°)	Symmetry Code	SE_{G09} kcal/mol	ρ ($eÅ^{-3}$)	$\nabla^2\rho$ ($eÅ^{-5}$)
3	C1–H1···F2	2.32	162	x+1, y, z	-4.8	0.07	1.11
	C14–H14···F4	2.30	161	x-1, y, z	-4.8	0.07	1.14
18F1	C1–H1···F1	2.44	156	x+1, y, z	-5.0	0.05	0.92
18F2	C1–H1···F1	2.35	168	x, y-1, z	-5.1	0.06	1.06
	C14–H14···F2	2.41	159	x, y+1, z	-5.1	0.05	0.97
36F1	C1–H1···F1	2.31	160	$1-x, -{}^{1}/_{2}+y, {}^{1}/_{2}-z$	-4.8	0.05	0.97
36F2	C1–H1···F1	2.37	173	x, y-1, z	-5.0	0.05	0.99
	C14–H14···F2	2.38	168	x, y+1, z	-5.1	0.05	0.99
6	C1–H1···F1	2.47	163	x-1, y, z	-4.1	0.04	0.77
21	C1–H1···F1	2.46	153	x+1,+y,+z	-5.3	0.05	0.82
	C3–H3···F1	2.66	149	x+1,+y,+z		0.03	0.60
39	C1–H1···F1	2.49	152	x-1,+y,+z	-4.9	0.05	0.87
	C3–H3···F1	2.64	150	x-1,+y,+z		0.03	0.56

52	C1–H1···F4	2.47	136	x+$^{1}/_{2}$, -y-2, z+$^{1}/_{2}$	-3.4	0.05	0.89
54	C1–H1···F4	2.52	162	x, y-1, z	-4.7	0.04	0.72
55	C1–H1···F4	2.34	166	x+1, y, z	-3.9	0.06	1.04
58	C1–H1···F8	2.63	145	x, -y+2, z+$^{1}/_{2}$	-4.0	0.03	0.59
59	C1–H1···F8	2.40	173	-x+$^{1}/_{2}$, -y+$^{1}/_{2}$, -z	-3.5	0.05	0.90
60	C1–H1···F4	2.40	173	-x+$^{1}/_{2}$,-y+$^{1}/_{2}$, -z	-4.4	0.04	0.71
61	C1–H1···F4	2.53	166	x-1, y, z	-5.0	0.04	0.71
71	C1–H1···F4	2.66	173	-x+1, y-$^{1}/_{2}$, -z	-4.1	0.03	0.53
	C9–H9···F4	2.54	122	-x+1, y-$^{1}/_{2}$, -z		0.04	0.80
77	C14–H14···F5	2.45	167	-x, -y+1, -z+2	-2.8	0.04	0.75
	C22–H22···F5	2.58	134	-x, -y+1, -z+2		0.04	0.73
83	C1–H1···F4	2.47	162	x-1, -y+$^{1}/_{2}$, z-$^{1}/_{2}$	-2.1	0.05	0.86
	C9–H9···F4	2.53	148	x-1, -y+$^{1}/_{2}$, z-$^{1}/_{2}$		0.04	0.83

Thus, it can be concluded that when one of the F atoms of the A ring is present at the *ortho*-position, the formation of synthons mentioned in figure 1 becomes highly likely. But, it also depends on the position of F atoms on the B ring. As we have observed that when the position of F on the B ring is either *para*- or *meta* in case of difluoro substituted system (C.N. 1 to 15, reference no. 23) and 3,4 or 3,5 in case of tetrafluoro substituted system; then the synthons I(A) or I(C) have been found in the crystal lattices of the respective compounds. Moreover, the presence of F on the B ring at 2,3; 2,4; 2,5 and 2,6 positions removes the possibility of formation of these synthons. The only exception to this trend is seen in the cases of compounds **71**, **77** and **83** where the synthon I(B) has been found in their crystal structures, even when the position of F atom on the B ring is 2,4; 2,5 or 2,6. Furthermore, these dimers provide high stabilization energies (SE_{G09}) (generally >3.5 kcal/mol) along with the higher values of electron densities at their BCPs (0.03-0.07 e Å^{-3}) indicating that C–H···F–C interactions are of closed shell nature just like other weak hydrogen bonds (C–H···O–C and C–H···N–C). All these synthons are actually the building blocks to form a chain of molecules in the crystal lattice.

Result of CSD Calculation:

Based on the interaction table 1, it is seen that distances and angles of C–H···F hydrogen bonds in the above studied dimers lie in the range of 2.4 to 2.7 Å and 130^{o} to 170^{o} respectively. Therefore, searches were done for the synthons I(A), I(B) and I(C) in the CSD (CSD Version 5.35, May-2014 update) with the following set of search criteria:

(**a**) H···F distance range: 2.4 to 2.7 Å, (**b**) ∠C–H···F range: 130^{o} to 170^{o}, (**c**) 3D coordinates determined, (**d**) R factor (≤ 0.1), (**e**) Not disordered, (**f**) No errors, (**g**) Not Polymeric, (**h**) No ions, (**i**) No powder structures, (**j**) Only Organics

23 hits have been found with the synthon I(A) and 1 and 2 hits were found for the synthons I(B) and I(C) respectively. Out of these, three compounds having synthon I(A) and one compound for each of synthons I(B) and I(C) were chosen for the calculation of stabilization energies using G09 and MP2 level of theory with 6-31+G(d) basis set as was done for our molecules. From the table 2, it is evident that the stabilization energies (and H···F distances and ∠C–H···F–C angles) for the molecules having synthon I(A) significantly match with the stabilization energies and the geometric parameters observed in the molecules studied by us. The only representative of synthon I(B) available from the database has two occurrences of the synthon I(B) and two C–H···N–C hydrogen bonds as well to form the dimer. Subsequently the stabilization energy of the dimer of this molecule (CSD REFCODE RICMOG) is much higher than the others. On the other hand, one out of two hits for the synthon I(C) shows much lower stabilization due to poor directionality (∠C–H···F < 140°).

Table 2: Details of the geometrical parameters for the C–H···F hydrogen bonds and their interaction energies.

Synthon	Code	*d* (H···F/Å)	θ (∠C–H···F/°)	SE_{G09} kcal/mol
IA	**YAJHIC**	2.54	148	-3.7
	BANGOM02	2.52	164	-3.2
	AYUSAP	2.63	156	-3.7
IB	**RICMOG**	2.52	170	-11.6
		2.66	140	
IC	**MIGPAU04**	2.40	129	-1.7
		2.61	130	

Synthon II: This synthon consists of two C–H···F–C hydrogen bonds through one donor and one acceptor present in each of the interacting molecule forming an eight membered ring [$R_2^2(8)$] (figure 5). This synthon can be categorized into two groups:

- *Head to head or tail to tail dimers*: In this particular case, both the interacting atoms belong to the same ring.
- *Head to tail dimers*: In this case, the atoms of the *B ring* participate in the interaction with the atoms of the *A ring*.

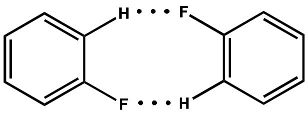
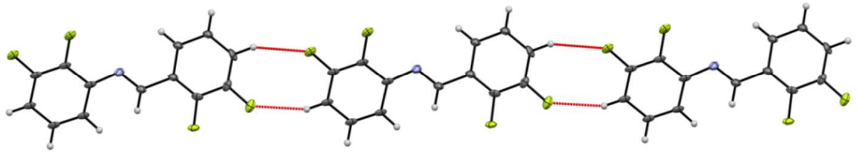


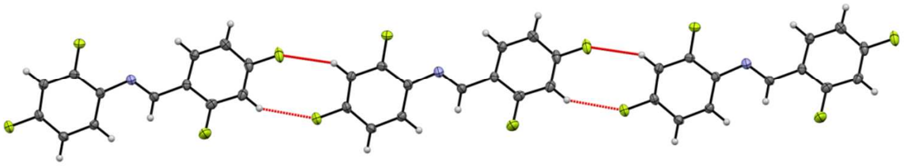
Figure 5: A schematic representation of the synthon II $[R_2^2(8)]$

When the positions of the substituents at both the rings are either 2,3-2,3 (**64**) or 2,4-2,4 (**71**); **head to tail dimers** have been found. Further, similar dimers have also been seen in the compounds **61** (2,6-3,5) and **86** (2,6-3,4) (figure 6, table 3) with the same substitutions (2,6) on B ring and different substitutions (3,4 and 3,5) on the A ring. It is noteworthy that the dimers found in **64** and **71** are different from those observed in **61** and **86** in terms of the spatial arrangements of the interacting molecules.

Head to tail dimers:



CN **64**: **2,3-diF(B)-2,3-diF(A)**



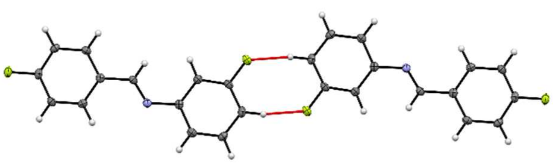
CN **71**: **2,4-diF(B)-2,4-diF(A)**

CN **61**: **2,6-diF(B)-3,5-diF(A)** CN **86**: **2,6-diF(B)-3,4-diF(A)**

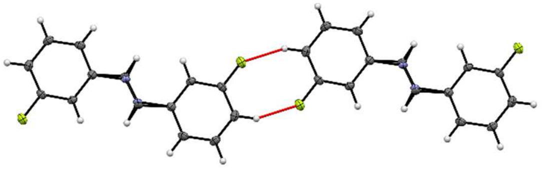
Figure 6: formation of synthon II (head to tail dimers) in the compounds **64**, **71**, **61** and **86**.

Head to head and tail to tail dimers have also been observed in the structures of the studied system (figure 7, table 3). These dimer were also observed in difluoro substituted *N*-benzylideneaniline in the compounds with one fluorine at the *meta*- position of A ring and other at the *para*- or *meta*- position of B ring (figure 7, table 3). These head to head, tail to tail and head to tail dimers are building blocks of molecular chains or ribbons in the lattice. Although synthon II was found to be more abundant in our compounds, the stabilization energies of the dimers formed by synthon II were found to be lower (generally < 2.5 kcal/mol) than those observed in the cases of dimers formed by the synthons I(A), I(B) and

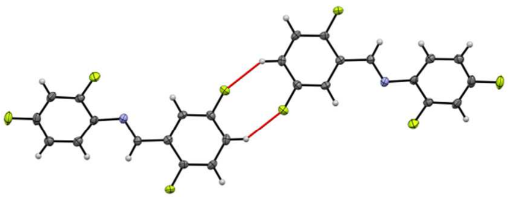
I(C). Both the electron density and Laplacian at the BCPs for these dimers were found to be lower than those observed in the dimers formed by the synthons I(A), I(B) and I(C). This indicates that the C–H···F–C interactions responsible for the synthon II are marginally weaker than the same in the synthons I(A), I(B) and I(C).



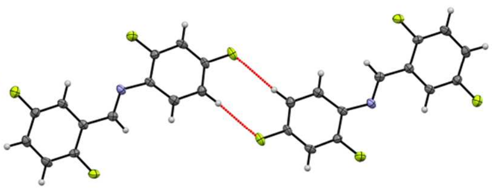
CN **2**: **4-F(B)-3-F(A)**



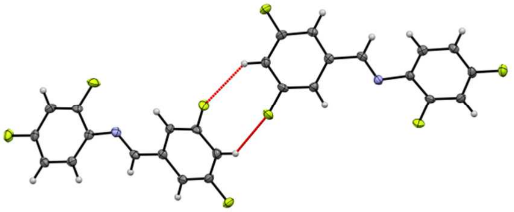
CN **5**: **3-F(B)-3-F(A)**



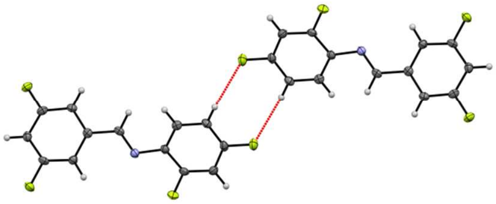
CN **77**: **2,5-diF(B)-2,4-diF(A)**



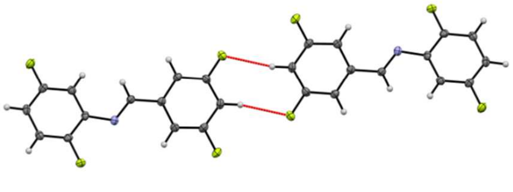
CN **77**: **2,5-diF(B)-2,4-diF(A)**



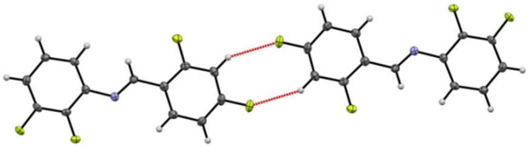
CN **59**: **3,5-diF(B)-2,4-diF(A)**



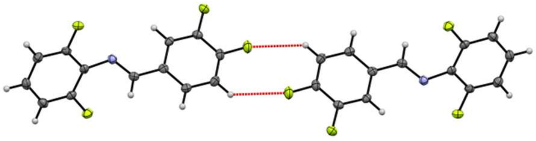
CN **59**: **3,5-diF(B)-2,4-diF(A)**



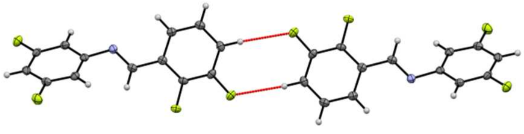
CN **60**: **3,5-diF(B)-2,5-diF(A)**



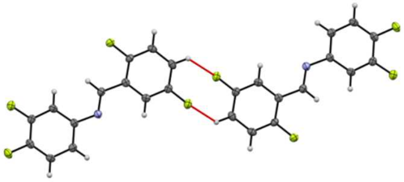
CN **70**: **2,4-diF(B)-2,3-diF(A)**



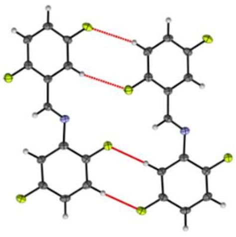
CN **55**: **3,4-diF(B)-2,6-diF(A)**



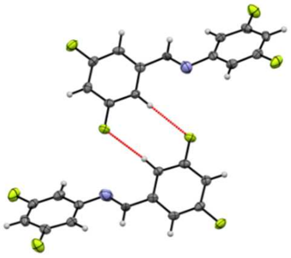
CN **69**: **2,3-diF(B)-3,5-diF(A)**



CN **80**: **2,5-diF(B)-3,4-diF(A)**



CN **78**: **2,5-diF(B)-2,5-diF(A)**



CN **63**: **3,5-diF(B)-3,5-diF(A)**

Figure 7: Formation of synthon III (head to head and tail to tail dimers) in the compounds **2**, **5**, **77**, **59**, **60**, **70**, **55**, **69, 80, 78,** and **63**.

It is noteworthy that the compound **57** has two molecules A (ordered) and B (disordered) in the asymmetric unit. The ordered molecules pack through synthon II, while the disordered molecules don't do the same and also don't form any C–H···F hydrogen bonds involving the disordered F atoms [figure S5(a)-(d)].

Table 3: Details of the geometrical parameters for all the C–H···F hydrogen bonds, the values of electron densities and Laplacians at their BCPs

Code	**C–H···F**	***d*** **(H···F/Å)**	**θ (∠C–H···F/°)**	**Symmetry Code**	**SE$_{G09}$ kcal/mol**	***ρ*** **(eÅ^{-3})**	**$\nabla^2\rho$ (eÅ^{-5})**
64	C18–H18···F8	2.69	149	x+1, y-1,z+1	-2.1	0.02	0.51
	C24–H24···F6	2.49	158	x-1, y+1,z-1		0.04	0.79
71	C4–H4···F3	2.47	146	x-1, y,z+1	-1.7	0.04	0.82
	C12–H12···F2	2.67	131	x+1, y,z-1		0.03	0.56
61	C3–H3···F3	2.47	169	-x,+y+1/2,-z+1/2	-2.5	0.04	0.88
	C10–H10···F1	2.65	168	-x,+y-1/2,-z+1/2		0.03	0.57
86	C4–H4···F3	2.66	134	-x+1,-y,-z+1	-4.7	0.03	0.61
	C9–H9···F1	2.70	134	-x+1,-y,-z+1		0.03	0.56
55	C4–H4···F1	2.66	138	3-x, -y, 1-z	-2.0	0.03	0.55
59	C10–H10···F3	2.53	147	-x,-y+1,-z	-2.0	0.04	0.77
	C5–H5···F2	2.56	138	-x+1, y,-z+$^{1}/_{2}$	-1.6	0.03	0.69
60	C5–H5···F1	2.56	138	-x+1,+y,-z+$^{1}/_{2}$	-1.3	0.04	0.75
	C11–H11···F3	2.66	162	-x+$^{1}/_{2}$,y+$^{1}/_{2}$,-z+$^{1}/_{2}$	-2.0	0.03	0.54
70	C4–H4···F2	2.52	151	1-x,-1-y,1-z	-1.9	0.04	0.73
	C11–H11···F3	2.63	160	-x,-y,-z+2	-2.3	0.03	0.59
69	C5–H5···F2	2.69	161	-x+1,-y+1,-z	-1.9	0.04	0.66
2	C11–H11···F2	2.55	134	-x,1-y,-z	-1.6	0.04	0.70
5	C5–H5···F1	2.53	135	-x+2, -y, -z+1	-1.5	0.04	0.68
77	C10–H10···F3	2.59	162	-x+1,-y+2,-z+1	-2.1	0.03	0.67
	C18–H18···F6	2.53	133	-x,-y+2,-z+1	-2.1	0.04	0.77
80	C5–H5···F2	2.63	125	-x+1,-y+2,-z	-1.9	0.03	0.65
66	C12–H12···F3	2.45	153	x-1,+y,+z	-3.8	0.04	0.84
	C9–H9···F4	2.44	154	x+1,+y,+z		0.04	0.86
78	C12–H12···F3	2.59	155	x+1, y, z	-4.2	0.03	0.66
	C9–H9···F4	2.57	154	x-1, y, z		0.04	0.70
	C7–H7···F1	2.63	147	x+1, y, z		0.03	0.60
	C4–H4···F2	2.64	147	x-1, y, z		0.03	0.60
63	C20–H20···F2	2.50	175	x-$^{1}/_{2}$,-y,z	-2.0	0.03	0.68
	C7–H7···F6	2.57	168	x+$^{1}/_{2}$, -y, z		0.04	0.78

Result of CSD Calculation:

A CSD (CSD Version 5.35, May-2014 update) search was done on the synthon II with the similar distance and angle ranges and set of criteria that were used for the synthons

I(A), I(B) and I(C). Among the 277 hits from this search, 14 simple molecules were selected for stabilization energy computation as was done before. Once again, it was found that the stabilization energies for these dimers were in the range of -1.5 to -2.8 kcal/mol.

Table 4: Details of the geometrical parameters for the C–H···F hydrogen bonds and their interaction energies.

Code	*d* (H···F/Å)	θ (∠C–H···F/°)	SE_{G09} kcal/mol
ABAKIZ	2.69	141	-1.5
ATOZOY	2.68	135	-1.7
BESZUW	2.53	143	-1.51
CICTOY	2.65	152	-2.38
DIBCOH	2.67	160	-2.51
DUTREQ	2.67	148	-2.82
ENUKAA	2.61	143	-1.61
QOSBAC	2.56	147	-1.85
RAGFAI	2.62	146	-2.38
ROFPUY	2.63	154	-1.68
SESTOB	2.62	138	-1.36
ULELUT	2.63	145	-1.83
UREKIM	2.45	156	-1.56
YICFEX01	2.58	152	-1.20

Synthon III: This is a variation of synthon II, where both the donors are present on one interacting molecule, while both the acceptors are present in the other molecule, thereby generating a new synthon III [$R_2^2(8)$] (figure 8).

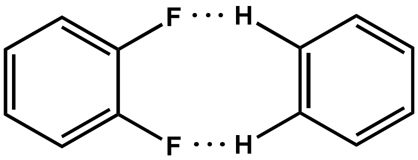
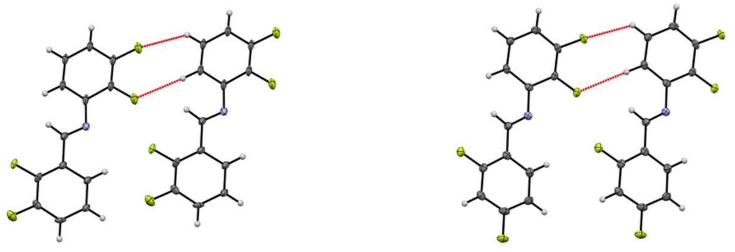


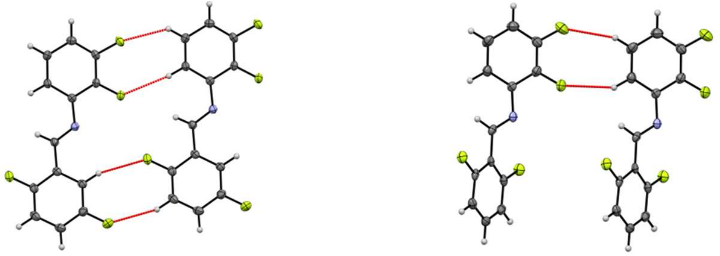
Figure 8: A schematic representation of the synthon III [$R_2^2(8)$]

In our system, this type of synthon is possible with 2,3-difluoro and 3,4-difluoro substituted compounds. Among the possible 20 such molecules, only 6 of them were found to contain synthon III. When the two F atoms were present at 2,3 position in the A ring, then the compounds **64**, **70**, **76** and **82** with F substitutions at 2,3; 2,4; 2,5; and 2,6 respectively, display synthon III (figure 9, table 5).

In addition to these, synthon III has also been found in the compounds **55** and **86**, where the positions of the substituents on one of the ring are 3,4 and on the other ring are 2,6 (figure 10, table 5). The rest of the molecules having two adjacent fluorine atoms either preferred synthon I(A, B and C) or synthon II or were found to be non-centrosymmetric and were packed by other weak hydrogen bonds (ESI, structural descriptions of the compounds 52 to 54, 56 to 58, 62, 65 to 69, 74, 76, 80, 82, 86).

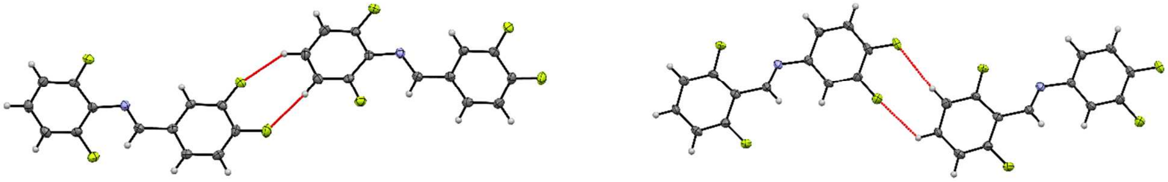


CN **64**: **2,3-diF(B)-2,3-diF(A)** CN **70**: **2,4-diF(B)-2,3-diF(A)**



CN **76**: **2,5-diF(B)-2,3-diF(A)** CN **82**: **2,6-diF(B)-2,3-diF(A)**

Figure 9: formation of synthon III in the compounds **64**, **70**, **76** and **82**.



CN **55**: **3,4-diF(B)-2,6-diF(A)** CN **86**: **2,6-diF(B)-3,4-diF(A)**

Figure 10: Formation of synthon III in the compounds **55** and **86**.

From the table 5, it is observed that the stabilization energies for the dimers having synthon III are between -1.9 and -4.3 kcal/mol. Two C–H···F–C interactions in this synthon being dissimilar in nature, two H···F distances and two ∠C–H···F–C angles have been found to be different in each compound. The C–H···F–C interactions with shorter H···F distances are associated with smaller ∠C–H···F–C angles. This synthon in **64**, **70** and **76** are seen to be more stabilizing (SE_{G09} > 3 kcal/mol), while the same for the other three are found to be less stabilizing (SE_{G09} < 3 kcal/mol).

Table 5: Details of the geometrical parameters for all the C–H···F–C hydrogen bonds, the values of electron densities and Laplacians at their BCPs

Code	**C–H···F**	***d*** **(H···F/Å)**	**θ** **(∠C–H···F/°)**	**Symmetry Code**	**SE$_{G09}$ kcal/mol**	***ρ*** **(eÅ^{-3})**	**$\nabla^2\rho$** **(eÅ^{-5})**
64	C10–H10···F2	2.48	134	x-1, y, z	-4.2	0.04	0.82
	C9–H9···F1	2.58	172			0.03	0.65
70	C10–H10···F3	2.49	127	x+1, y, z	-3.2	0.04	0.84
	C9–H9···F4	2.61	166			0.03	0.62
76	C4–H4···F2	2.63	155	x+1, y, z	-4.3	0.03	0.59
	C10–H10···F3	2.48	136			0.04	0.81
	C9–H9···F4	2.57	172			0.03	0.67
	C7–H7···F1	2.62	155	x-1,y,z		0.03	0.59
82	C10–H10···F3	2.67	159	x+1, y, z	-2.6	0.03	0.57
	C9–H9···F4	2.63	149			0.03	0.52
55	C11–H11···F2	2.60	127	x,-y+$^1/_2$,z-$^1/_2$	-1.9	0.03	0.66
	C10–H10···F1	2.59	168			0.03	0.64
86	C6–H6···F4	2.69	159	x,y,z-1	-1.9	0.03	0.52
	C5–H5···F3	2.63	120			0.03	0.66

Result of CSD Calculation:

A similar CSD search was done on this synthon. Out of 49 hits found, stabilization energies have been calculated for seven of them (table 6). The stabilization energies of these dimers vary from -1.0 to -3.6 kcal/mol.

Table 6: Details of the geometrical parameters for the C–H···F–C hydrogen bonds and their interaction energies.

Code	***d*** **(H···F/Å)**	**θ** **(∠C–H···F/°)**	**SE$_{G09}$ kcal/mol**
ASIJER	2.63	142	-1.0
	2.66	151	
HORVOA	2.60	157	-1.0
	2.66	148	
MIKGOD	2.59	144	-1.5
	2.62	157	
AKUNOK	2.67	164	-1.1
	2.52	138	
PUGDEB	2.60	142	-1.6
	2.58	144	
HORVUG	2.53	156	-1.0
	2.59	139	
UCOVEN	2.42	169	-3.6
	2.64	138	

Synthon IV: The 4th most common synthon was also observed in our previous studies.[23,25] It is a dimer (figure 11) formed when one fluorine atom was present at the *ortho* position of the B ring and the other halogen (F, Cl or Br) on the A ring was present at the *meta* position, thereby forming a ring $[R_2^2(13)]$. As described in our earlier report, this synthon remained unchanged upon replacement of non-interacting F with Cl or Br (figure 12). We have further found that this synthon remains unaltered even on the addition of fluorine atoms at the *meta* or *para* position of both the phenyl rings (figure 13 and 14).

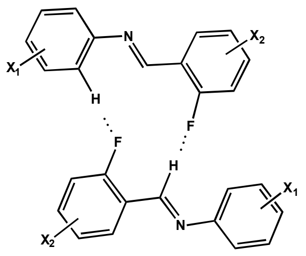
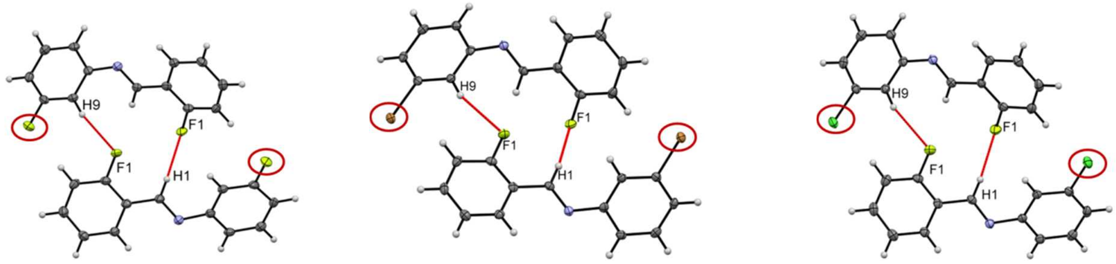


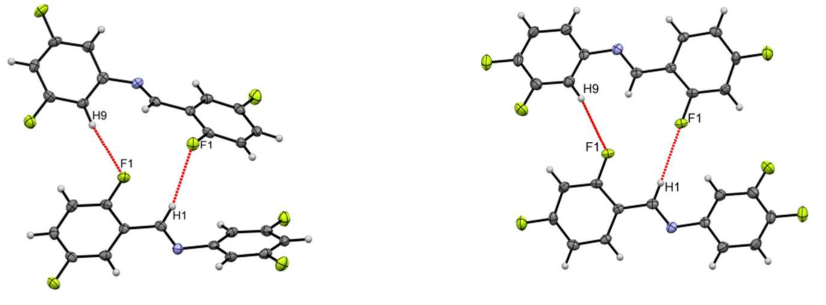
Figure 11: A schematic representation of the synthon IV $[R_2^2(13)]$.

Dihalogen substituted *N*-benzylideneanilines: In this system, synthons formed are shown below



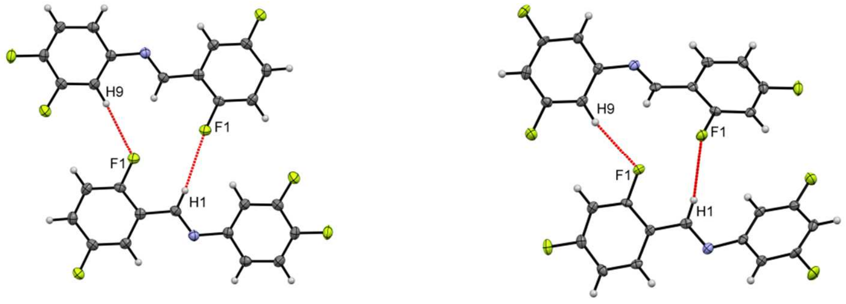
CN **8**: **2F(B)-3F(A)** CN **23**: **2F(B)-3Br(A)** CN **32**: **2F(B)-3Cl(A)**

Figure 12: Formation of synthon IV in the compounds **8**, **23**, and **32.**



CN **81**: **2,5-diF(B)-3,5-diF(A)** CN **73**: **2,4-diF(B)-3,4-diF(A)**

Figure 13: Formation of synthon IV in the compounds **81** and **73** (Addition of fluorine at the *m* or *p*-position of both the rings)



CN **80**: **2,5-diF(B)-3,4-diF(A)**   CN **75**: **2,4-diF(B)-3,5-diF(A)**

Figure 14: Formation of synthon IV in the compounds **80** and **75** (Addition of fluorine at the *m*-position of one phenyl ring and at the *p*-position of second phenyl ring and vice-versa)

This synthon is highly specific for this model system. Therefore, CSD search was performed on this synthon. But, it is noteworthy that the dimers formed by this synthon are highly stabilizing in nature. The interaction energies offered by these dimers have been found to be > 4 kcal/mol and the value of electron densities and Laplacian are supportive for moderately strong C–H···F–C hydrogen bonds (table 7).

Table 7: Details of the geometrical parameters for all the C–H···F–C hydrogen bonds, the values of electron densities and Laplacians at their BCPs

Code	C–H···F	*d* (H···F/Å)	θ (∠C–H···F/°)	Symmetry Code	SE_{G09} kcal/mol	ρ (eÅ^{-3})	$\nabla^2\rho$ (eÅ^{-5})
8	C9–H9···F1	2.55	169	$-x+1, y-{}^1/_2, -z+{}^1/_2$	-4.8	0.04	0.73
	C1–H1···F1	2.67	157			0.03	0.58
32	C9–H9···F1	2.61	164	$-x+2, y-{}^1/_2, -z+{}^3/_2$	-5.3	0.03	0.63
	C1–H1···F1	2.69	155			0.03	0.55
50	C9–H9···F1	2.66	163	$-x+2, y+{}^1/_2, -z+{}^3/_2$	-4.8	0.03	0.57
	C1–H1···F1	2.70	154			0.03	0.53
73	C9–H9···F1	2.76	134	-x+1,-y,-z+1	-3.9	0.02	0.48
	C1–H1···F1	2.66	172			0.02	0.46
75	C9–H9···F1	2.51	169	$x-{}^1/_2,-y+{}^3/_2,-z$	-3.9	0.04	0.78
	C1–H1···F1	2.71	162			0.02	0.48
80	C9–H9···F1	2.59	161	-x,-y+1,-z	-4.9	0.03	0.63
	C1–H1···F1	2.66	164			0.02	0.51
81	C9–H9···F1	2.48	172	$x+{}^1/_2,-y-{}^1/_2,-z-2$	-4.7	0.04	0.82
	C1–H1···F1	2.51	148			0.03	0.60

In addition to these four frequently occurring synthons, a $[R_2^2(10)]$ dimer has also been found in **74**, where the C–H···F–C contacts are always between the ordered regions of the molecule and the disordered regions have not made any contribution in the overall packing of the molecules (figure S19).

Results of Stabilization Energies and AIM Calculations: We have plotted a 3D graph (figure 15) between the distance, angle and interaction energies of the dimers, which had only one C–H···F–C interaction between the two interacting molecules (table S32 in ESI). A minimum in the energy surface has been found at a distance between 2.60-2.65 Å with the angle close to 170° (figure 15). The table containing all the values of distances, angles, interaction energies and topological properties of the interacting dimers has been given in ESI (table S31).

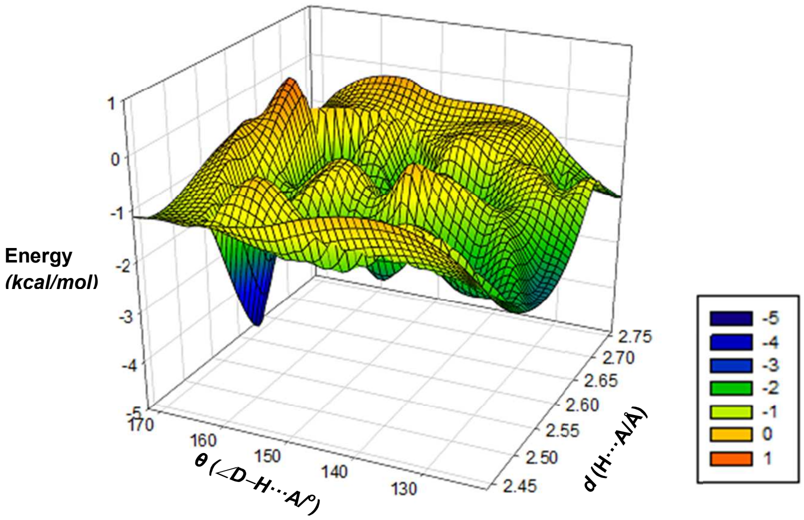
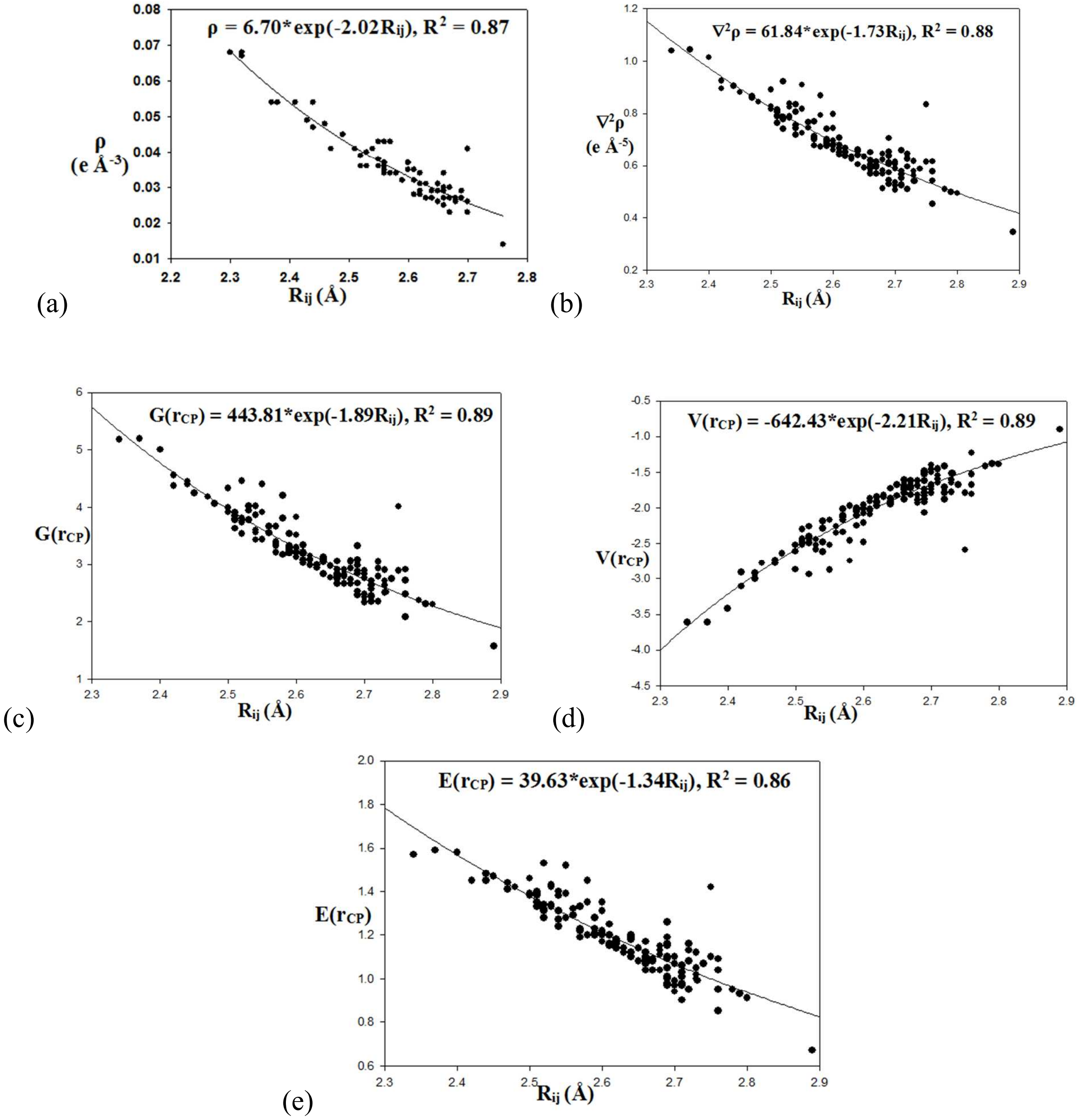


Figure 15: 3D plot between the distances, angles and energy for C–H···F–C hydrogen bond, which have been found to form in the crystal lattice of the studied compounds.

The topological parameters [ρ, $\nabla^2\rho$, $V(\mathbf{r}_{\mathrm{CP}})$, $G(\mathbf{r}_{\mathrm{CP}})$ and $E(\mathbf{r}_{\mathrm{CP}})$] at the (3, -1) bond critical point of C–H···F–C hydrogen bonds have been found to have exponential variation with the bond path, as was reported by us in the system of dihalogen substituted *N*-benzylideneanilines[25], thus representing a weak hydrogen bond type of interaction. These plots along with the fitted equations and the corresponding values of R^2 have been given in figure 16 and the values of these parameters are given in table S31 (ESI).



(a) (b)

(c) (d)

(e)

Figure 16: 2D plot between **(a)** *ρ* vs R$_{ij}$, **(b)** $\nabla^2\rho$ vs R$_{ij}$, **(c)** $G(\mathbf{r}_{CP})$ vs R$_{ij}$, **(d)** $V(\mathbf{r}_{CP})$ vs R$_{ij}$, and **(e)** $E(\mathbf{r}_{CP})$ vs R$_{ij}$, (b)

Conclusions:

The above structural analyses has shown that weak hydrogen bonds involving fluorine are capable of forming frequently occurring supramolecular synthons, which were consistent in difluoro, fluoro-bromo, fluoro-chloro and tetrafluoro substituted *N*-benzylideneanilines. The formation of synthons has been correlated with the nature (F/Cl/Br) and positions of the substituents. The strength, directionality and structure directing ability of these synthons have been confirmed by replacing one of the F atoms by heavier halogen atoms (Cl or Br) or by the addition of more F atoms to the same system. The stabilization energy of these dimers has been found to be between 2-6 kcal/mol. The nature of C–H···F–C interactions is confirmed to be weak hydrogen type from the plots between their topological properties versus the bond path. Moreover, the 3D plot (figure 15) has shown that the interaction energy is maximum for more directional C–H···F–C hydrogen bonds with angle close to 170° and distance between 2.6-2.65 Å. These observations provide evidences for the stable, directional and to some extent predictable C–H···F–C hydrogen bonds and also emphasize the structure directing capability of the supramolecular synthons based on C–H···F–C hydrogen bonds in the molecular systems without the possibility of strong hydrogen bonds.

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A comprehensive understanding of the synthons involving C–H···F–C hydrogen bond(s) from structural and computational analyses

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