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Experimental and computational analysis of supramolecular motifs involving Csp2(aromatic)-F and CF3 group in organic flustrates

Piyush Panini\textsuperscript{a}, Rajesh G. Gonnade\textsuperscript{b}, Deepak Chopra\textsuperscript{a}\textsuperscript{*}

\textsuperscript{a} Crystallography and Crystal Chemistry Laboratory, Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Madhya Pradesh, India-462066. Fax: 91-0755-6692370. Email: dchopra@iiserb.ac.in

\textsuperscript{b} Center for Materials Characterization (CMC), CSIR-National Chemical Laboratory, Pune-411008, India.

Abstract:

A detailed experimental (SCXRD) and theoretical (PIXEL and QTAIM) investigation of the evolution of different supramolecular motifs formed via the presence of both C(sp\textsuperscript{2})/sp\textsuperscript{3}-F group in the crystal packing have been performed in a series of newly synthesized substituted benzanilides (containing “both” the fluorine and the trifluoromethyl group in the same molecule) along with previously reported similarly related crystal structures [CrystEngComm, 2008, 10, 54–67; CrystEngComm, 2012, 14, 1972–1989, CrystEngComm, 2013, 15, 3711–3733]. It was observed that the highest stabilized molecular motifs primarily consist of C(sp\textsuperscript{2})-H···F-C(sp\textsuperscript{2}) H-bond in preference to C(sp\textsuperscript{2})-H···F-C(sp\textsuperscript{3}) H-bond in the crystal. The motifs involving C(sp\textsuperscript{2})-H···F-C(sp\textsuperscript{2})/(sp\textsuperscript{3}) H-bonds were observed to be present over the entire distance range between 2.2 to 2.7Å, albeit the difference in energies of stabilization involving fluorine atoms attached to sp\textsuperscript{2} and sp\textsuperscript{3} carbon is not significant in molecular crystals. From QTAIM analysis, the C(sp\textsuperscript{2})/(sp\textsuperscript{3})-F···F-C(sp\textsuperscript{2})/(sp\textsuperscript{3}) interactions were observed to be closed shell in nature and provide local stabilization, indicating the formation of bond, similar to weak hydrogen bonds observed in crystals.

Introduction:

The introduction of a fluorine atom to the carbon atom (termed as “Organic Fluorine”) can lead to the formation of many weak interactions like C-H···F=C hydrogen bond [1-2], C-F···F-C [3-4]
and C-F···π [5-7] interactions and study of these interactions involving organic fluorine is still an expanding area of research amongst the scientific community [8]. However, there has been an enduring discussion regarding the ability of organic fluorine to act as a hydrogen bond acceptor [9 - 18] because of its low polarizability. However, crystal structure analysis of fluorobenzenes [12] and ribonucleic acids [13] unfasten the area of research regarding the study of interactions involving organic fluorine. Further, such interactions with the protein active site through C–F···C=O, and C–F···H–Cα interactions have been reviewed by Diedrich et. al. [19]. Since then many studies via inputs from crystallography, spectroscopy and theoretical calculations have established the fact that the interactions involving fluorine are ubiquitous and can play an important role in the stabilization of the crystal packing and influence the phenomenon and properties in the solids state, one such example is polymorphism. The extensive literature on compounds related to the presence of organic fluorine has been excellently combined in reviews [8, 20-22] and a book chapter [23]. It was initially postulated that the weak interactions involving fluorine like C-H···F-C hydrogen bonds are only significant in the absence of any other strong intermolecular forces [24]. The analysis of the nature of fluorine interactions on many molecules has been performed, wherein the possibility of the formation of strong hydrogen bonds was eliminated. Amongst these, benzene [12, 18], naphthalene, anthracene and phenanthrene [16], isoquinolines [24-25], trifluoroacetophenones [26], N-phenylmaleimides and corresponding phthalimides [27], benzonitriles [28], pyridines [29], azobenzenes [30], N-benzylideneanilines [31-32], toluene [33], N-methyl-N-phenylbenzamides [34] are a few examples to be mentioned. There is not sufficient literature on the study of these intermolecular interactions in molecules wherein strong intermolecular forces are present [20]. However, fluorinated N-(2-Chloropyridin-4-yl)-N'-phenylureas [35], fluoro-N-(pyridyl)benzamides [36], fluorine-substituted benzoic acid [37], fluorine-substituted benzimidazoles [38] are a few examples wherein evaluation of interactions involving fluorine were realized in the presence of a strong hydrogen bond. Keeping in mind the above-mentioned points, improvements aimed towards the understanding of the nature, capability and energetics of interactions involving organic fluorine (in particular C-H···F and C-F···F-C interactions) in the presence of strong hydrogen bond has been undertaken by our research in the past last few years [17, 39 - 41]. Our main goal was (i) a systematic exploration of the participation of the fluorine atom in different intermolecular interactions (ii) robustness of the interaction (i.e how often they are present) in the formation of different supramolecular
motifs (iii) role of hybridization of C-atom to which fluorine is attached and finally (iv) calculation of stabilization energy and topological parameters such as the electron densities ($\rho$), Laplacian ($\nabla^2\rho$), local potential energy ($V_b$), kinetic potential energy ($G_b$) at the bond critical point by Quantum Theory of Atoms in Molecules (QTAIM) [42]. In this regard, a large library of molecules containing the organic fluorine group have been synthesized, crystallized and investigated for different intermolecular interactions involving organic fluorine. The systems were designed such that these only have one strong donor and acceptor (the amide group -NH-C=O in our works) atom which connects at least one phenyl ring wherein the position of the fluorine (connected to C-atom) of different hybridization, [C($sp^2$)-F & C($sp^3$)-F$_3$ group] many vary, keeping the main molecular connectivity invariant. Hence, different molecules, namely fluorine substituted benzanilides [17], fluorine and -CF$_3$ substituted N-phenylacetamides and N-methylbenzamides [39], -CF$_3$ substituted benzanilides have been studied [40]. The purpose of selecting the CF$_3$ group was as follows: (i) The –CF$_3$ group being strongly electron-withdrawing in nature increase the acidity of hydrogen atoms in its vicinity (ii) better H-bond acceptor abilities of C($sp^3$)-F can be exploited (iii) in addition to C-H···F-C hydrogen bonds, the propensity of formation of other interactions namely C-F···F-C and C-F···π is now increased (iv) in addition to all the above-mentioned points, a comparative study about the role of hybridization of the C-atom to which fluorine is attached can be achieved in the crystal.

Therefore, we have synthesized a library of substituted benzanilides (eighteen in number) containing both the fluorine and trifluoromethyl group on the same molecule (Scheme 1). Initial investigations on two molecules in this series, namely N-(4-fluorophenyl)-3-(trifluoromethyl) benzamide and 4-fluoro-N-[3-(trifluoromethyl)phenyl]benzamide, demonstrated existence of short H-bonds with organic fluorine in the presence of strong N-H···O=C H-bonds [41]. The nature of these interactions was tested with criteria for H-bond proposed recent by IUPAC [43] and has also been analyzed by the PIXEL method [44 - 47] and the QTAIM approach [42]. It is now well established that the C-H···F interactions at short distances are indeed a “true H-bond” and these are not the consequence of crystal packing. In this current work, along with the detailed crystal packing analysis of the remaining newly synthesized compound in this series, our main focus will be on the (i) identification of different robust or reoccurring motifs formed by the interactions involving organic fluorine in the crystal (ii) investigations of these in terms of their nature, energetics and topological properties by the PIXEL method and the QTAIM
approach (iii) comparative study about the role of hybridization [48] of the C-atom to which fluorine is attached, based on the inputs obtained from current and previous series of molecules [17, 39–40] having similar molecular framework.

**Experimental section:**

All the compounds were synthesized by the procedure that is already reported in the literature [40]. Scheme 1 describes the general route for the synthesis of all the 18 compounds and their corresponding nomenclature code used in this paper. All the synthesized compounds were characterized by FTIR [Fig. S1(a)-(p)], and $^1$H NMR [Fig. S2(a)-(p)] (Section S1). Melting points were recorded with DSC [Fig. S3(a)-(p)] on the pure powder compounds. Powder X-ray diffraction (PXRD) data were recorded for all the solid compounds and then compared with their calculated PXRD patterns [Fig. S4(a)-(p)]. In order to ensure the phase purity, a profile fitting refinement (Section S2) was performed using JANA2000 [49]. In the case of 1F2T, 2F3T, 2T1F and 3T1F, high values of the profile fitting parameters (Rp, Rwp) were observed, which may indicate the possibility of the presence of more than one phase in the bulk powder.

The details on all the crystallization experiments of all the solid compounds from different solvents and solvent mixtures are presented in the ESI (Table S1).

**Data collection, structure solution and refinement**

Single crystal X-ray diffraction data were collected on Bruker AXS SMART APEX II CCD diffractometer at 100 K. All the data were collected at 100(2) K. All the crystal structures were solved by direct methods using SIR 92 [50] and refined by the full matrix least-squares method using SHELXL2013 [51] present in the program suite WinGX [52]. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms bonded to C and N atoms were positioned geometrically and refined using a riding model with $U_{iso}(H) = 1.2U_{eq}[C(sp^2)]$. The disorder associated with the CF$_3$ group (in case of compounds 2F2T and 2T1F-w) and positional disorder of F-atom (in case of compounds 1F1T, 2F1T, 2F2T, 2T1F, 2T1F-w and 2T2F) were modeled with PART command in SHELXL 2013 at two independent orientations (major component was labeled ‘A’) (Fig. S5, ESI). Molecular and packing diagrams were generated using Mercury software [53]. Table S2 lists all the crystallographic and refinement data. ORTEPs of all compounds were presented in Figures S5(a) – S5(m) in the ESI.
Scheme 1: Synthetic scheme for all the compounds along with their nomenclature plan used in this manuscript are presented.

Computational tools and theoretical calculations:

PIXEL method [in CLP computer program package (version 10.2.2012)] has been used for the interaction energy of the selected molecular pairs, extracted from the crystal packing and related by the corresponding symmetry element as mentioned in our previous work [41]. In the method, the total interaction energy is partitioned into their Coulombic ($E_{\text{coub}}$), polarization ($E_{\text{pol}}$), dispersion ($E_{\text{disp}}$) and repulsion ($E_{\text{rep}}$) contributions. In case of disordered molecules, the molecular conformation with the maximum population was considered for the calculations. PIXEL method was observed to provide better and useful insights towards the nature of different types of intermolecular interactions present in the different molecular pairs/motifs [54–57]. The PIXEL interaction energy was further compared with the interaction energies obtained from theoretical calculations at DFT+Disp/B97D [58–59] level at higher aug-cc-pVTZ basis set using TURBOMOLE [60]. The hydrogen atoms were moved to neutron values (1.083 Å for C–H) before the calculations. The basis set superposition error (BSSE) for the interaction energies was
corrected by using the counterpoise method [61]. Table S3 (divided into two parts: S3a and S3b, separately for C-F···F-C in Table S3b) lists the selected intermolecular interactions (in the decreasing order of their stabilization energy) in different motifs along with their interaction Energies (I.E.) of the motifs. In case of highly disordered compounds 2T1F_w [having rotational disorder associated with CF₃ group and positional disorder of the fluorine atom at the phenyl ring along with the presence of half molecule of water in the asymmetric unit, Fig. S5(h)], PIXEL calculation have not been performed. Instead, BSSE corrected interactions energies for the selected dimers were calculated at DFT+Disp/B97D level using aug-cc-pVTZ basis set (Table S5).

Analysis of Topological Parameters (QTAIM calculations)
Topological calculations on the selected dimers at the crystal geometry were performed with same procedure as mentioned previously [41] using AIMALL (version 13.05.06) [62]. The selected topological parameters like electron densities (ρᵦ), Laplacian (∇²ρᵦ), local potential energy (Vᵦ), and kinetic energy density (Gᵦ) at the bond critical points (BCPs) were calculated. The dissociation energies for the different intermolecular interactions were also estimated through the following two empirical approaches: (i) D. E^{V} (int) = −0.5 Vᵦ (in atomic units) [63] and (ii) D.E^{G} (int) = 0.429 Gᵦ (in atomic units) [64 - 65]; where D.E(int) is the dissociation energy of the interaction. Interaction energy (I.E) = −D.E. Vᵦ and Gᵦ are the local potential and kinetic energy density at the bond critical points (BCPs), respectively. The results of the topological analysis on the different molecular pairs are presented in section S4 (Table S4 & S5) in ESI. Topological parameters of for the selected C-H···F and C-F···F-C interactions in different motifs along with their dissociation energy is presented in Table S4b. Compounds having disorder associated with CF₃ group or fluorine (positional disorder) were not considered for the calculations except for 1F1T and 2T2F wherein the positional disorder of fluorine with occupancy ratio at the two positions were observed to be 0.875(2):0.125(2) and 0.944(3):0.056(3) respectively. In these cases, the molecular conformation with the maximum population was considered for the calculations.
Results and Discussions:

1) *N*-\((2\text{-fluorophenyl})\)-2-(trifluoromethyl)benzamide (1F1T):

The compound 1F1T crystallizes in the orthorhombic non-centrosymmetric space group *Pna*₂₁ with *Z* = 4. A strong N-H···O=C H-bond along with a weak C-H···π hydrogen bond (motif I, -12.7 kcal/mol, **Table S3a**) was observed to connect the molecules along the crystallographic *a*-axis in the formation of the molecular chain [**Fig. 1 (a)**]. Such chains are interconnected via weak C-H···F-C₃sp hydrogen bond (motif V, -1.5 kcal/mol). Furthermore, there exists formation of the herringbone pattern observed down the *bc* plane in the crystal packing, stabilized via the presence of motif II (involving C-H···O, C-H···F-C₃sp₂ hydrogen bond, -6.2 kcal/mol) and weak C-H···F-C₃sp hydrogen bonds in motif IV (-1.9 kcal/mol). Weak C-H···O=C and C-H···F-C₃sp hydrogen bonds were found to stabilize the crystal packing (motif III, -4.8 kcal/mol) in the generation of a molecular chain [**Fig. 1(c)**]. It is to be noted that the stabilization energy for a C-H···F hydrogen bond was reported to be ~ -0.40 kcal/mol (-1.6 kJ/mol) by *ab initio* theoretical calculation for the neutral molecule by D’Oria & Novoa [56].

The presence of weak C-H···F-C hydrogen bonds in the motifs III, IV and V were characterized topologically by using the QTAIM approach. There were presence of (3, -1) bond critical points (BCPs) recognized for these interactions (**Table S4b**) along with other related interactions present in the respective motifs [**Fig. 1(d)**].
Figure 1(a): Packing of molecules in 1F1T via the network of strong N-H···O=C, weak C-H···π and C-H···F-C\(_{sp3}\) hydrogen bonds. The Roman numbers in red (in this and also subsequent diagrams) indicate the molecular motifs presented in the Table S3. (b) Formation of the herringbone layer of molecules down the \(bc\) plane with the utilization of weak C-H···O, C-H···F-C\(_{sp2}\) and C-H···F-C\(_{sp3}\) hydrogen bonds in 1F1T. (c) Formation of the molecular chain in 1F1T via weak C-H···O and C-H···F-C\(_{sp3}\) hydrogen bonds. (d) Selected molecular motifs (denoted with Roman number from Table S4) in 1F1T, showing different intermolecular interactions. The brown small spheres represent bond critical points (BCPs) on the bond path.
2) \(N\)-(3-fluorophenyl)-2-(trifluoromethyl)benzamide (2F1T):

The compound \(2F1T\) crystallizes in the monoclinic centrosymmetric space group \(P2_1/c\) with three molecules in the asymmetric unit \((Z' = 3)\) (Fig 2). Two (molecule 2 and 3) out of three molecules in the asymmetric unit observed in the formation of the most stabilized molecular motif I (-13.3 kcal/mol) involving strong N-H\(\cdots\)O=C, weak C-H\(\cdots\)π and C-H\(\cdots\)F\(C_{sp3}\) hydrogen bonds along with π\(\cdots\)π interactions. Selected molecular pairs, which contribute towards the stabilization of the crystal packing in \(2F1T\), are presented in Figure 2(c) along with their interaction energies (I.E). The three most stabilized molecule motifs I, II (-13.1 kcal/mol) and III (-12.2 kcal/mol), consisting of strong N-H\(\cdots\)O=C hydrogen bond along with other weak interactions (Table S3a) were observed to be involved in the formation of a molecular chain along the crystallographic \(a\)-axis in the crystal packing [Fig. 2(a) and (b)]. Such chains were observed to be connected with the utilization of the motif IV, V and VII in the crystal packing [Fig. 2(a)]. The motif IV (I.E = -5.3 kcal/mol) consists of short C-H\(\cdots\)O=C (2.39Å/ 149°) and C-H\(\cdots\)π (2.68Å/ 141°) hydrogen bond while the motif V (-4.7 kcal/mol) involves the presence of weak C-H\(\cdots\)F\(C_{sp3}\) hydrogen bond [Fig. 2(a)] along with π\(\cdots\)π interactions. A short C-H\(\cdots\)F\(C_{sp3}\) (2.39Å/ 127°) and a weak C-H\(\cdots\)π (2.86Å/ 155°) hydrogen bond were recognized to connect the molecules in motif VII. Moreover, the packing of molecules in \(2F1T\) are also stabilized by the presence of weak C-H\(\cdots\)F\(C_{sp2}\) hydrogen bond in the motifs VIII, IX and XI with the stabilization energy ranging from -1.3 to -2.6 kcal/mol [Table S3, Fig. 2(c)]. It is to be noted that the motif X, involves the presence of bifurcated \(C_{sp2}-F\cdots F-C_{sp3}\) interactions [Type I (2.883Å, 110°, 94°) and other a “near” Type II (3.133Å, 152°, 83°) contact], provides stabilization towards the crystal packing with interaction energy of 1.7 kcal/mol, the nature being primarily of dispersive origin. A very recent charge density analysis has revealed the polarization of the electron density on the fluorine atoms on the trifluoromethyl group which facilitate the formation of type II C-F\(\cdots\)F-C contacts in the crystal [67]. Furthermore, a very short type I \(C_{sp2}-F\cdots F-C_{sp3}\) interaction [2.736Å, 146°, 149°, motif XII] were observed in the crystal packing, providing almost negligible stabilization [0.1 kcal/mol] [Fig. 2(c)]. This stabilization energy is similar with the value reported in a recent analysis by \textit{ab initio} calculations on all the unique dimers, extracted from the crystal structure of CF\(_4\), C\(_2\)F\(_4\) and C\(_6\)F\(_6\) by Osuna \textit{et al.} [68].
Figure 2(a): Packing of molecules in 2F1T via the network of strong N-H···O=C, weak C-H···π and C-H···F-Csp3 hydrogen bonds. (b) Clear depiction of the ...123... molecular chain along the crystallographic a-axis. Different color codes of carbon atoms indicate the presence of three molecules in the asymmetric unit. Grey: Molecule 1, Purple: Molecule 2 and Green: Molecule 3. (c) Selected molecular pairs extracted from the crystal packing of 2F1T along with their interaction energies (Table S3).
3) *N*-(2-fluorophenyl)-3-(trifluoromethyl)benzamide (1F2T):

The compound 1F2T crystallizes in the monoclinic centrosymmetric space group with *Z* = 4. Figure 3(a) depicts the packing of molecules in 1F2T in all the three directions with the utilization of different molecular motifs I to VIII (Table 2). The highest stabilized molecular motif I (I.E = -11.8 kcal/mol) consists of strong N-H···O=C, a short and directional C-H···F-C<sub>sp2</sub> (2.47Å, 168°) and a short C-H···π (2.66Å, 158°) hydrogen bond along with a C-F···π interactions. The motif I along with motif III [I.E = -4.8 kcal/mol; consists of a short C-H···π (2.61Å, 159°) and C-H···O=C hydrogen bond] and motif V (I.E = -1.9 kcal/mol; involves a bifurcated C-H···F-C<sub>sp3</sub> along with the presence of C-F···π interactions) were observed to pack the molecules along the *c*-axis with the utilization of *c*-glide perpendicular to *b*-axis. A short and directional C-H···F-C<sub>sp2</sub> (2.45Å, 168°) hydrogen bond along with the two π···π interactions in the motif II (-6.4 kcal/mol) were observed to connect the molecules along the crystallographic *a*-axis. The molecular chains, formed along the *a*-axis, with the utilization of motif II [Fig. 3(b)], were observed to be connected *via* motifs IV, VI to VIII in the generation of a molecular layer down the *ab* plane. Amongst these, motif VI (-1.5 kcal/mol) and VII (-1.1 kcal/mol) were found to consist of a short C-H···F-C<sub>sp3</sub> (2.47Å, 161°; 2.57Å, 139°) hydrogen bond while the motif IV (I.E = -2.0kcal/mol), involves dimeric C<sub>sp3</sub>-F···F-C<sub>sp3</sub> interaction and a weakly stabilized (-0.2 kcal/mol) motif VIII consists of type I C<sub>sp3</sub>-F···F-C<sub>sp3</sub> (2.942Å, 158°, 158°) interactions. Further, QTAIM calculations, reveal the presence of a (3, -1) BCP for all C-H···F and C-F···F-C interactions [Fig. 3(c)].
Figure 3(a): Packing of the molecules down the \( bc \) crystallographic plane in \( 1F2T \) via the network of strong \( N-H\cdots O=C \), weak \( C-H\cdots \pi \), \( C-H\cdots F_{sp2} \) and \( C-H\cdots F_{sp3} \) hydrogen bonds along with \( \pi\cdots \pi \), \( C_{sp3} - F\cdots \pi \) and \( C_{sp3} - F\cdots F_{sp3} \) interactions. (b) Part of the crystal packing in \( 1F2T \) down the \( ab \) plane, displaying the presence of weak \( C-H\cdots F_{sp2} \) and \( C-H\cdots F_{sp3} \) hydrogen bonds along with \( \pi\cdots \pi \) (off set) and \( C_{sp3} - F\cdots F_{sp3} \) interactions. (c) Selected molecular motifs (denoted with Roman number from Table S4) in \( 1F2T \), showing different intermolecular interactions. The small brown spheres represent bond critical points (BCPs) on the bond path. Only the interacting part of the motifs was shown in case of IV, VI – VIII.

4) \( N-(3\text{-fluorophenyl})-3\text{-}(\text{trifluoromethyl})\text{benzamide (2F2T)}: \)

The compound \( 2F2T \) crystallizes in the orthorhombic centrosymmetric space group \( Pbcn \) with \( Z = 8 \). The most stabilized molecular motif \( I \) (I.E = -12.1 kcal/mol) consists of strong \( N-H\cdots O=C \) hydrogen bond supported by weak \( C-H\cdots O \), and \( C-H\cdots \pi \) hydrogen bonds. A molecular chain, formed via motif \( I \) utilizing \( c \)-glide, were observed to connect via the weak \( C-H\cdots \pi \) hydrogen bonds recognized in the motif \( II \) (-4.2 kcal/mol), \( VI \) (-2.1 kcal/mol), \( VIII \) (-1.6 kcal/mol) [Fig 4(a)]. Furthermore, packing of molecules in \( 2F2T \) were stabilized by the formation of motifs \( III \) (-3.0 kcal/mol) and \( IV \) (-2.4 kcal/mol), comprising of dimeric weak \( C-H\cdots F_{sp3} \) hydrogen bonds. It is of interest to note that a short and directional \( C_{sp3} - F\cdots \pi \) [3.134Å, 150°, Table S3] interaction, utilizing 2 fold rotation parallel to \( b \)-axis, provided (motif \( V \) ) stabilization to the crystal packing [2.3 kcal/mol] with dispersion being a major contributor. Moreover, a bifurcated weak \( C-H\cdots F_{sp2} \) hydrogen bonds (motif \( VII \), -1.7 kcal/mol) were realized in the formation of a molecular chain, utilizing a \( c \)-glide plane perpendicular to the \( b \)-axis. Such chains were connected with the presence of motif \( IX \) (-0.2 kcal/mol), possessing a pair of weak type \( I \) \( C_{sp3} - F\cdots F_{sp3} \) interactions including the one at short distance (2.873Å, 122°, 122°) [Fig. 4(b)]. It was also noticed that the two sides of the phenyl ring, substituted with the fluorine and \(-CF_3 \) group, were observed in the formation of different supramolecular motifs in the crystal packing [Fig. 4(c)].
**Figure 4(a):** Packing of molecules in 2F2T via the network of strong N-H⋯O=C, weak C-H⋯O, C-H⋯π hydrogen bonds. (b) Packing of molecules in 2F2T, displaying the network of strong N-H⋯O=C, weak C-H⋯O, C-H⋯F-C\textsubscript{sp2} and C-H⋯F-C\textsubscript{sp3} hydrogen bonds along with C\textsubscript{sp3}-F⋯F-C\textsubscript{sp3} interactions. (c) Part of crystal packing in 2F2T, depicting the presence of different motifs involving fluorine interactions.

5) *N*- (3-fluorophenyl)-4-(trifluoromethyl)benzamide (2F3T):

The compound 2F3T was found to crystallize in the monoclinic centrosymmetric space group C\textsubscript{2}/c with Z = 8. The strong N-H⋯O=C hydrogen bond along with the weak C-H⋯O=C hydrogen bond and π⋯π interactions (Motif I, -12.3 kcal/mol) was observed to engage in the formation of molecular chains along the crystallographic b-axis. Such chain is connected by the utilization of weak C-H⋯π hydrogen bonds and π⋯π interactions in the formation of a molecular layer down the bc plane [Fig. 5(a)], involved in the next three stabilized motifs II (-7.6 kcal/mol), III (-7.4 kcal/mol) and IV (-6.1 kcal/mol). Packing of molecules down the bc plane [Fig. 5(b)] was detected as the formation of a molecular sheet with utilization of bifurcated weak and short C-H⋯F-C\textsubscript{sp3} hydrogen bonds [2.55 Å, 145° (motif VIII, -1.3 kcal/mol); 2.55 Å, 125° (motif IX, -1.1 kcal/mol)], along the b-axis. Furthermore, the crystal packing of 2F3T was also observed to be stabilized by the formation of similarly stabilized molecular motifs V (-2.2 kcal/mol) and VI (-2.1 kcal/mol) [Fig. 5(c)]. The motif V consists of bifurcated weak C-H⋯F-C\textsubscript{sp2} hydrogen bonds while the motif VI involves in the formation of dimeric C\textsubscript{sp3}-F⋯F-C\textsubscript{sp3} interactions. In addition, a type II C\textsubscript{sp3}-F⋯F-C\textsubscript{sp3} interaction (motif VII, -1.9 kcal/mol) were also observed to form a chain, utilizing 2\textsubscript{1} screw axis along the crystallographic b-axis in the crystal packing [Fig. 5(d)]. The selected motifs, containing weak C-H⋯F and C\textsubscript{sp3}-F⋯F-C\textsubscript{sp3} interactions, were characterized by the QTAIM theory and the presence of (3, -1) BCPs were observed on the bond path of these interactions [Fig. 5(e), Table S5].
Figure 5(a): Formation of a molecular layer down the $bc$ crystallographic plane with the utilization of strong N-H···O=C, weak C-H···π hydrogen bonds and π···π interactions in 2F3T. (b) Packing of molecules down the $ab$ plane via the networks of strong N-H···O=C and weak C-H···F-$C_{sp3}$ hydrogen bonds in 2F3T. (c) Part of the crystal packing in 2F3T, displaying the formation of bifurcated weak C-H···F-$C_{sp2}$ hydrogen bonds and dimeric $C_{sp3}$-$F$···F-$C_{sp3}$ interactions. (d) Part of the crystal packing 2F3T showing the presence of $C_{sp3}$-$F$···F-$C_{sp3}$ interactions forming a chain motif along with a strong N-H···O=C hydrogen bond. (e) Selected molecular motifs (Table S4) in 2F3T, showing different intermolecular interactions. The small brown spheres represent bond critical points (BCPs) on bond path. Only interacting part of the motif was shown in case of VI - IX.
6) \(N-(4\text{-}fluorophenyl)-4\text{-}(trifluoromethyl)benzamide (3F3T):\)

The compound 3F3T crystallizes in the triclinic centrosymmetric space group \(P\mathbf{1}\) with \(Z = 2\). As expected, the most stabilized molecular motif I \((-11.7\text{ kcal/mol})\) was noticed to involve strong N-H\(\cdots\)O=C hydrogen bond along with weak C-H\(\cdots\)O=C hydrogen bond and \(\pi\cdots\pi\) interactions. The motif I was found to involve in the formation of molecular chain along the crystallographic \(a\)-axis. Such chains were interlinked via dimeric weak C-H\(\cdots\)F-C\(_{sp2}\) hydrogen bonds [motif VII \((-1.4\text{ kcal/mol})\) and VIII \((-1.1\text{ kcal/mol})\)] and dimeric weak C\(_{sp3}\)-F\(\cdots\)F-C\(_{sp3}\) interactions [motif IX \((-0.7\text{ kcal/mol})\)] in the formation of a molecular layer down the \(ab\) plane. Further, in the molecular packing of 3F3T, the molecular chains formed with the utilization of motif VIII and IX, were observed to be connected by the molecular motifs II to VI which consist of other weak interactions in the crystal packing [Fig. 6(b)]. The motif II involves the presence of a weak C-H\(\cdots\pi\) hydrogen bond and a short C\(_{sp3}\)-F\(\cdots\)O=C (3.118Å, 120°) interaction, the interaction energy being -6.1 kcal/mol. The motif III and IV were noticed to provide similar stabilization towards the crystal packing (-4.7 kcal/mol and -4.0 kcal/mol respectively) but observed to involve different interactions. The motif III consist of weak C-H\(\cdots\)F-C\(_{sp3}\) and C-H\(\cdots\pi\) hydrogen bonds while the weak \(\pi\cdots\pi\) interaction was observed in motif IV. Moreover, a dimeric short C-H\(\cdots\)F-C\(_{sp3}\) (2.45Å, 157°) contact were observed to stabilize (motif V, -2.8 kcal/mol) the crystal packing in 3F3T. In addition, a dimeric weak C\(_{sp3}\)-F\(\cdots\pi\) interactions (motif VI, -2.2 kcal/mol) were also observed to provide stabilization to the crystal packing in 3F3T. The weak interactions involving fluorine in 3F3T were studied with QTAIM theory and the presence of (3, -1) BCP were observed for these interactions in their corresponding molecular motifs [Fig. 6(c)].
Figure 6(a): Packing of molecules in 3F3T down the ab crystallographic plane with the utilization of strong N-H⋯O=C, weak C-H⋯O=C, C-H⋯F-C\textsubscript{sp2} hydrogen bonds along with C\textsubscript{sp2}-F⋯F-C\textsubscript{sp2}, C\textsubscript{sp3}-F⋯F-C\textsubscript{sp3} and π⋯π interactions. (b) Packing of molecules in 3F3T down the bc crystallographic plane via weak C-H⋯F-C\textsubscript{sp2}, C-H⋯F-C\textsubscript{sp3} and C-H⋯π hydrogen bonds along with C\textsubscript{sp2}-F⋯F-C\textsubscript{sp2}, C\textsubscript{sp3}-F⋯F-C\textsubscript{sp3}, C\textsubscript{sp3}-F⋯O=C, C\textsubscript{sp3}-F⋯π and π⋯π interactions. (c) Selected molecular motifs (Table S4) in 3F3T, showing different intermolecular interactions. The small brown spheres represent bond critical points (BCPs) on bond path. Only interacting part of the motif was shown in case of III, V – VII, IX and X.
7) 2-fluoro-N-(3-(trifluoromethyl)phenyl)benzamide (2T1F):

The compound 2T1F crystallizes in the centrosymmetric orthorhombic space group \textit{Pbca} with \( Z = 8 \). A strong N-H\cdots O=C hydrogen bond along with \( \pi \cdots \pi \) interactions (motif I, -11.6 kcal/mol check this value) was observed in the generation of a \textit{zig-zag} chain with the utilization of \( b \)-glide perpendicular to the \( a \)-axis. The chains are interconnected utilizing motif VII which consist of the weak near \textit{type II} \( C_{sp^3} \cdot \cdot \cdot F_{sp^3} \) (2.990\AA, 108°, 154°) interactions (I.E. being -1.0 kcal/mol). The next most stabilized motif II (-4.5 kcal/mol), consisting of weak \( \pi \cdots \pi \) interaction, was found to connect the molecular chain [\textit{Fig. 7(b)}] generated \textit{via} 2\_1-screw along \( b \)-axis utilizing weak C-H\cdots \pi hydrogen bond (Motif V, -2.8 kcal/mol). Furthermore, there was formation of a herringbone pattern down the \( ac \) plane [\textit{Fig. 7(c)}] observed in the crystal packing of 2T1F, exploiting motif III, IV and VI. The motif III (-3.0 kcal/mol) was noticed to involve weak C-H\cdots O and C-H\cdots F-C_{sp^3} hydrogen bond while it was short bifurcated C-H\cdots F-C_{sp^2} hydrogen bonds which were observed in the motif IV, the stabilization energy being 2.8 kcal/mol. Moreover, a weak C-H\cdots F-C_{sp^3} hydrogen bond was recognized in the motif VI (-1.4 kcal/mol).
Figure 7(a): Packing of molecules in \textit{2T1F} \textit{via} strong N-H⋯O=C hydrogen bonds along with C\textit{sp}3-F⋯F-C\textit{sp}3 and π⋯π interactions. (b) Packing of molecules in \textit{2T1F} \textit{via} the network of weak C-H⋯π hydrogen bonds and π⋯π interactions. (c) Formation of a molecular layer in \textit{2T1F} down the \textit{ac} crystallographic plane with the utilization of \textit{via} weak C-H⋯O, C-H⋯F-C\textit{sp}2 and C-H⋯F-C\textit{sp}3 hydrogen bonds.
8) 2-fluoro-N-(3-(trifluoromethyl)phenyl)benzamide hydrate (2T1F_w):

Hydrate of the compound 2-fluoro-N-(3-(trifluoromethyl)phenyl)benzamide hydrate (2T1F_w) crystallizes in the orthorhombic centrosymmetric space group Pbcn with half molecule of water in the asymmetric unit (Table S2). It has been characterized using differential scanning calorimetry (DSC), thermal gravimetry analysis (TGA) and hot stage microscopy (HSM) (Section S3 in ESI). Packing of the molecules in 2T1F_w were observed to be stabilized by the solvent molecule with the formation of strong hydrogen bonds like N-H···O_water and O_water-H···O=C, noticed in motif I and II with I.E. being -5.04 kcal/mol and -5.63 kcal/mol respectively [Table S3c, Fig. 8(a)]. A stacked motif III along a- axis (utilizing 21-screw), consisting of two weak C-H···F-C_sp3 hydrogen bonds along with π···π interactions, is a highly stabilized (-14.2 kcal/mol) molecular pair in the crystal packing [Fig 8(a), Table S3c]. The packing of the molecules down the bc plane shows the formation of a molecular layer utilizing the motif I, II, IV and V [Fig 8(b)]. The molecular chain with alternate interactions of the compound and solvent was observed to be connected with weak C-H···F-C_sp3 hydrogen bond (motif V, -1.64 kcal/mol) utilizing c-glide perpendicular to b-axis [Fig. 8(b)]. Moreover, the presence of highly short type I C_sp3-F···F-C_sp3 interactions were recognized in the weakly stabilized molecular motif VI (-0.42 kcal/mol) and relatively destabilized motif VII (+1.29 kcal/mol) (Table S3c). It is to be noted here that the molecules in the destabilized motif VII, consisting of highly short type I C_sp3-F···F-C_sp3 interactions (2.663Å, 132°, 132°), was observed to be stabilized by the presence of water molecule via the formation of two strong O_water-H···O=C hydrogen bonds (motif II) in the crystal packing [Fig. 8(a)].
9) 2-fluoro-N-(4-(trifluoromethyl)phenyl)benzamide (3T1F):

The compound 3T1F crystallizes in the non-centrosymmetric orthorhombic space group \( P2_1cn \) with \( Z = 4 \). Packing of molecules in 3T1F involve the formation of a molecular chain along the \( b \)- axis with the utilization of strong N-H\cdots O=C along with weak C-H\cdots O=C hydrogen bond and \( \pi \cdots \pi \) interactions (motif I, -9.7 kcal/mol, Table S3). Such chains are interconnected by the utilization of next two similarly stabilized motifs II (-6.5 kcal/mol) and III (-6.3 kcal/mol) in the formation of a molecular layer down the (101) plane [Fig. 9(a)]. The motif II involved a pair of weak C-H\cdots \pi hydrogen bonds along with a short \( C_{sp^3}-F\cdots C_{sp^3} \) (2.840Å, 127°, 171°) and a short \( C_{sp^3}-C\cdots O \) (3.134Å, 146°) interactions (Table S3) whereas a short and directional C-H\cdots \pi (2.65Å, 156°) and C-H\cdots F-C_{sp^3} (2.56Å, 160°) hydrogen bonds were present in motif III. Furthermore, a molecular chain formed by the utilization of bifurcated C-H\cdots F-C_{sp^3} hydrogen bonds (motif IV, -1.9 kcal/mol, 2\_1 screw parallel to \( a \)-axis) were observed to be interconnected via the motif II, III and V in the packing of molecules down the \( ac \) plane in 3T1F. The motif V (-1.6 kcal/mol) was found to consist of weak C-H\cdots F-C_{sp^3} hydrogen bonds. These were presence of (3, -1) BCPs identified in case of weak C-H\cdots F and C-F\cdots F-C interactions [Fig. 9(c), Table S4].
Figure 9(a): Packing of molecules in 3T1F via the network of strong N-H···O=C, weak C-H···π, and C-H···F-Csp3 hydrogen bonds along with Csp3-F···Csp3, Csp2-F···C=O and π···π interactions. (b) Packing view down the ac plane in 3T1F via the network of weak C-H···π and C-H···F-Csp3 hydrogen bonds along with Csp3-F···Csp3, Csp2-F···C=O interactions. (c) Selected molecular motifs (Table S4) in 3T1F, showing different intermolecular interactions. Only interacting part of the motif was shown in case of IV – V.
10) 3-fluoro-N-(2-(trifluoromethyl)phenyl)benzamide (1T2F):

The compound 1T2F crystallizes in the centrosymmetric monoclinic space group $P2_1/c$ with two molecules in the asymmetric unit ($Z = 8$). The two most and similarly stabilized molecular motifs I (-12.9 kcal/mol) and II (-12.4 kcal/mol) were observed to consist of strong N-H···O=C hydrogen bond along with short C$_{sp3}$-F···C=O (3.090Å, 141°; 3.011Å, 141° respectively, Table S3) and π···π interactions. These motifs were appeared to be involved in the formation of $...1212...$ type molecular chain along the crystallographic $a$-axis. Such chains are recognized to interlink with the exploitation of next four stabilized molecular motifs III, IV, V and VI.

In the similarly stabilized motifs III (-4.6 kcal/mol) and IV (-4.4 kcal/mol), there were short and directional C-H···O=C (2.33Å, 149°; 2.23Å, 168°) hydrogen bonds recognized with contribution from electrostatic (Coulombic + Polarization) was significant (46% and 54% respectively). Further, the motif V (involving a bifurcated weak C-H···F-C$_{sp3}$ and C-H···π hydrogen bonds) and VI (involving a bifurcated weak C-H···F-C$_{sp3}$ hydrogen bond) were observed to provide similar stabilization (-3.5 and -3.2 kcal/mol respectively) to the crystal packing. Moreover, intermolecular interactions involving organic fluorine of type C-H···F, C-F···F-C were noticed to stabilize the crystal packing in 1T2F and participate in the generation of different supramolecular motifs VII to XII (Table S3) in the crystal packing [Fig. 10(b) & 10(c)]. The motif VII (-2.8 kcal/mol) was observed to be composed of a dimeric weak C-H···F-C$_{sp3}$ hydrogen bonds along with dimeric C$_{sp3}$-F···F-C$_{sp3}$ interactions while a dimeric weak C-H···F--C$_{sp2}$ hydrogen bond, interacting side wise, was recognized in the equally stabilized motif VIII. Further, a bifurcated weak C-H···F-C$_{sp2}$ hydrogen bond was observed in motif IX (-1.8 kcal/mol) whereas in the similarly stabilized motif X (-1.7 kcal/mol), a short C-H···F-C$_{sp2}$ hydrogen bond (2.48Å, 137°) was recognized. In the last two weakly stabilized motifs XI (-1.1 kcal/mol) and XII (-0.6 kcal/mol), a weak C-H···F-C$_{sp2}$ hydrogen bond and weak type I C$_{sp3}$-F···F-C$_{sp2}$ interactions were observed respectively. All the molecular pairs consisting of weak C-H···F and C-F···F-C interactions were analyzed by the theory of QTAIM and the topological parameters were obtained (Table S4). There was presence of (3, -1) BCPs noticed for these interactions along with other related contacts in the respective motifs [Fig. 10(d)].
Figure 10(a): Formation of \textit{...\textit{1212}...} type molecular layer in 1T2F via strong N-H···O=C, weak C-H···π, and C-H···F-C\textsubscript{sp3} hydrogen bonds along with C\textsubscript{sp3}-F···C=O and π···π interactions. C-atoms in purple are shown for the second molecule in the asymmetric unit. (b) Packing view down the \textit{bc} plane, displaying network of weak C-H···π, C-H···F-C\textsubscript{sp2}, C-H···F-C\textsubscript{sp3} hydrogen bonds along with C\textsubscript{sp3}-F···F-C\textsubscript{sp3} interactions in 1T2F. (c) Packing of molecules in 1T2F via network of weak C-H···O, C-H···F-C\textsubscript{sp2}, C-H···F-C\textsubscript{sp3} hydrogen bonds along with C\textsubscript{sp3}-F···F-C\textsubscript{sp3} interactions. C-atoms in purple are shown for the second molecule in the asymmetric unit. (d) Selected molecular motifs (Table S4) in 1T2F, showing different intermolecular interactions. Only interacting part of the motif was shown in case of VII – XII.

11) 3-fluoro-N-(3-(trifluoromethyl)phenyl)benzamide (2T2F):

The compound 2T2F crystallizes in the non-centrosymmetric monoclinic space group Cc with four molecules in the unit cell. A strong N-H···O=C hydrogen bond along with π···π interactions (motif I, -11.3 kcal/mol) steer the molecules along [110] in the formation of a molecular chain. Such chains are interlinked with the involvement of next two stabilized motifs II (-5.5 kcal/mol) and III (-4.8 kcal/mol) in the crystal packing. The motif II was recognized to involve weak π···π interactions with substantial contribution from dispersion energy towards the total stabilization whereas a weak C-H···O=C along with two short C-H···F-C\textsubscript{sp2}/C\textsubscript{sp3} (2.45Å, 133°, 2.53Å, 136°)
respectively) hydrogen bonds were observed in motif III. Further the molecular ladder formed via the motif III was observed to be connected by the utilization of motifs IV, V and VI in the crystal packing [Fig. 11(b) & 11(c)]. The motif IV (-2.2 kcal/mol) consists of bifurcated weak C-H⋯F-C_{sp3} hydrogen bonds while a short C-H⋯F-C_{sp3} (2.50Å, 146°) hydrogen bond was observed in motif V (-1.5 kcal/mol). Moreover, a weak type I C_{sp3}⋯F⋯F-C_{sp3} interaction (motif VI, -1.2 kcal/mol) was also recognized to stabilize the packing the molecules in 2T2F (Table S3). The presence of (3, -1) BCPs were observed for the weak C-H⋯F and C-F⋯F-C interactions in the respective motifs [Fig. 11(d)].

**Figure 11(a):** Packing of molecules in 2T2F with the utilization of strong N-H⋯O=C, weak C-H⋯O, C-H⋯F-C_{sp2}, and C-H⋯F-C_{sp3} hydrogen bonds along with \( \pi \cdots \pi \) interactions. (b) Formation of a molecular layer down the bc plane by the utilization of weak C-H⋯O, C-H⋯F-C_{sp2}, and C-H⋯F-C_{sp3} hydrogen bonds and C_{sp3}⋯F⋯F-C_{sp3} interactions in 2T2F. (c) Packing of molecules in 2T2F via weak C-H⋯O=C, C-H⋯F-C_{sp2}, and C-H⋯F-C_{sp3} hydrogen bonds. (d) Selected molecular motifs (Table S4) in 2T2F, showing different intermolecular interactions. Only interacting part of the motif was shown in case of IV – VI.
12) 4-fluoro-N-(2-(trifluoromethyl)phenyl)benzamide (1T3F):

The compound 1T3F crystallizes in the centrosymmetric monoclinic space group $P2_1/n$ with two molecules in the asymmetric unit ($Z = 8$). The two most stabilized motifs I (-12.8 kcal/mol) and II (-12.7 kcal/mol), involving similar interactions (strong N-H···O=C hydrogen bond along with π···π interactions) were observe in the formation of a molecular chain of molecule 1 and 2 in the asymmetric unit respectively utilizing $n$-glide along $b$-axis [Fig. 12(a)]. Such chains are interconnected alternatively with the utilizations of motifs III, IV, V and VII. The motif III and IV provide similar stabilization (-4.4 kcal/mol and -4.1 kcal/mol respectively) and both are involved in the formation of highly short and directional C-H···O=C (2.29Å, 152°; 2.22Å, 167° respectively, Table S3) hydrogen bonds. A short C-H···F$_{sp^3}$ (2.56Å, 132°) along with a weak C$_{sp^3}$wH···π hydrogen bond were noticed to connect the molecules in motif V whereas a near type II along with a near type I C$_{sp^3}$wF···F$_{sp^2}$ interactions (2.983Å, 110°, 165°; 3.128Å, 90°, 117°) were recognized to stabilize (I.E being -2.7 kcal/mol) the crystal packing, existing as motif VII (Table 2). Further, packing of molecules in 1T3F stabilized the formation of two dimeric motifs VI (-3.3 kcal/mol) and VIII (-2.1 kcal/mol) [Fig. 12(b)]. The motif VI involved two C-H···F$_{sp^3}$ hydrogen bonds along with weak C$_{sp^3}$wH···F$_{sp^3}$ interactions (Table S3). And the dimeric motif VIII was observe to possess short C-H···F$_{sp^2}$ (2.48Å, 131°) hydrogen bond in the crystal packing in 1T3F. Moreover, there were three equally stabilized (1.5 kcal/mol) molecular motifs IX, X and XI observed in the crystal packing and all were noticed to involve weak C-H···F$_{Csp^2}$ hydrogen bonds (Table 2). Further a motif (XII, -1.3 kcal/mol), consisting of weak C$_{sp^2}$wH···F$_{sp^2}$-C$_{sp^2}$ interactions and connecting molecules ‘1’ of the asymmetric unit, was observed to stabilize the crystal packing in 1T3F [Fig. 12 (c)]. The weak C-H···F$_{Csp^2}$ hydrogen bonds and C-F···F$_{Csp^2}$ interactions, present in the motifs V to XII in 1T3F were characterized by the theory of AIM. There were presence of (3, -1) BCPs observed for these interactions [Fig. 12 (d)].
Figure 12(a) Packing of molecules in 1T4F via the network of strong N-H⋯O=C, weak C-H⋯O, C-H⋯π, and C-H⋯F;sp3;sp2 hydrogen bonds along with C;sp3;F⋯C=O and C;sp3;F⋯F;sp2;sp3 interactions. C-atoms in purple are shown for second molecule in the asymmetric unit. (b) Formation of molecular layer down the ac plane with the utilization of weak C-H⋯O=C, C-H⋯π, C-H⋯F;sp3;sp2 hydrogen bonds along with C;sp3;F⋯F;sp2;sp3 interactions in 1T3F. (c) Part of crystal packing in 1T3F, showing the presence of weak C-H⋯F;sp3;sp2 hydrogen bonds along with C-F⋯F-C interactions. (d) Selected molecular motifs (Table S4) in 1T3F, showing different intermolecular interactions. Only interacting part of the motif was shown in case of V - XII.

13) 4-fluoro-N-(4-(trifluoromethyl)phenyl)benzamide (3T3F):

The compound 3T3F crystallizes in the centrosymmetric monoclinic space group P21/c with Z = 4. A strong N-H⋯O=C hydrogen bond, supported by weak C-H⋯O=C and C-H⋯π hydrogen bond (motif I, 11.6 kcal/mol) was observed in the formation of a molecular chain utilizing c-glide perpendicular to b-axis in 3T3F [Fig. 13 (a) & 13(b)]. Such chains are interconnected via the motifs II, III, V and VIII. The weak π⋯π interactions were observed to connect molecules in the dimeric motifs II (-5.9 kcal/mol) and III (-4.6 kcal/mol). In the motif V (-2.6 kcal/mol), it was weak C-H⋯F-C;sp2 hydrogen bond along with C-H⋯C=O interactions were recognized whereas a short C-H⋯F-C;sp3;sp2 hydrogen bond was observed in motif VIII (-1.4 kcal/mol). The packing of the molecules in 3T3F involved the formation of a herringbone pattern down the crystallographic ab plane with the utilization of motifs IV [-2.7 kcal/mol; involving short C-H⋯π hydrogen bond (2.79Å, 133°; Table 2)], V and VIII [Fig. 13 (c)]. Moreover, a bifurcated C-H⋯F-C;sp2 hydrogen bond (motif VII, -2.2 kcal/mol), utilizing c-glide, was noticed in the formation of a molecular chain [Fig. 13 (d)]. The chain was interlinked via the presence of motifs VI, VIII and IX. The motif VI (-2.6 kcal/mol) was found to involve the weak C-H⋯F-C;sp3 hydrogen bond in the formation of a molecular chain utilizing c-glide [Fig. 13 (d)]. Dimeric and weakly stabilized (-0.4 kcal/mol) short C;sp3;F⋯F;sp3 interactions were identified in the motif IX. The molecular motif V- VIII and IX, consisting of weak interactions involving fluorine, were studied topologically using the approach of QTAIM. Bond critical points at the bond path for these interactions were observed [Fig. 13(e)].
Figure 13 (a): Packing of molecules in 3T3F via the network of strong N-H···O=C, weak C-H···O, C-H···π, C-H···F-C hydrogen bonds along with π···π interactions. (b) Depiction of a molecular chain via the motif I in 3T3F. (c) Formation of a layer down the ab plane, utilizing weak C-H···F-C hydrogen bonds and C-H···C=O interactions in 3T3F. (d) Formation of a weak bifurcated C-H···F-C hydrogen bonds along with C(sp3)F···F-C(sp3) interactions down the bc plane in 3T3F. (e) Selected molecular motifs (Table S4) in 3T3F, showing different intermolecular interactions. Only interacting part of the motif was shown in case of V - VII and IX.

Therefore, the detailed analysis of all crystal structure revealed that the C(sp²)/(sp³)-F group were observed in the formation of different robust structural motifs in presence of a strong N-H···O=C hydrogen bond and other related weak interactions like C-H···O=C, C-H···π, and π···π. Moreover, in many cases, different supramolecular motifs (Table S3) by C(sp²)/(sp³)-F from the both side of the molecules can combine co-operatively in the formation of bigger structural motifs in the crystal structures.

**Insights from Atoms in Molecules Calculations**

It is of interest to do topological characterization of H···F and F···F interactions, observed in this class of compounds (including the previously reported crystal structures [17, 38-40]) and
analysis of the nature of these interactions along with the relationship of different topological parameters at BCP with bond path length. For this purpose, the selected dimers involving H···F or F···F interactions were identified and QTAIM calculations have been performed at their crystal geometry in accordance with the procedure reported in our earlier work [40]. The results of the calculations are presented in Table S4 and S5 of Section S4 in ESI. Topological parameters for the selected C-H···F and C-F···F-C Interactions are given in Table S4b.

It is to be noted here that some of the important criteria for an interaction to be called a hydrogen bond or closed shell type are [69 -70]: (i) ρ value at BCP lies within the range [0.013, 0.270] e/Å³ (ii) Positive value of the Laplacian of the electron density [∇²ρ > 0]) indicates closed shell interactions (iii) The range of Laplacian values [0.578 < ∇²ρ (e/Å⁵) < 3.350] indicates the presence of a “H-bond” (iv) The value of |V_b|/G_b < 1 for hydrogen bond [71 -72] and closed shell interactions; V_b and G_b are the potential and kinetic energy density at BCP. It is of interest to validate the nature of H···F and F···F interactions with these criteria.

**Analysis of H···F bonding interactions**

H···F interactions were observed to lie in the range of 2.2Å – 3.0 Å for all structures in the current work. As observed earlier [40], the dependent of electron density (ρ_b) shows exponential dependence with the bond path length (r_ij) [Fig. 14(a)] with the values in the range of 0.085 > ρ_b > 0.015 e/Å³. Hence these fulfill the criterion for the interactions to be called a hydrogen bond. The dissociation energy of these interactions (vary exponentially with r_ij, [Fig. 14(b)]) were observed between ~3.0 to ~0.4 kcal/mol. The value of Laplacian observed to be positive [∇²ρ > 0), Fig. 14 (c)] for the entire bond path length (r_ij) suggesting the closed shell nature of these H···F interactions. It is to be noted that for short C-H···F bond path length (r_ij) at less than the sum of van der Waal radii [73] of H and F, 2.67 Å, the values of the Laplacian are in accordance with the Koch and Popelier criteria for the existence of hydrogen bond [74]. Moreover, the values of |V_b|/G_b were also observed to be less than one (criteria for hydrogen bond [71 -72]) for the entire range of bond path [Fig. 14 (d)].

Furthermore, it was of interest to study the role of hybridization of the C-atoms to which fluorine is attached in the C-H···F interactions. Hence the variation of dissociation energy (D.E) (kcal/mol) and electron density (e/Å³) at BCP and with H···F bond path length (Å) for C-H···F-C(sp²) and C-H···F-C(sp³) have been compared [Fig. 15(a) & 15(b), Table S4 and S5]. It was observed that the highest stabilized molecular motifs primarily consist of C(sp²)-H···F-C(sp²)
hydrogen bond in preference to $C(sp^2)$-H⋯F-$C(sp^3)$ hydrogen bond in the crystal with the difference in energies of stabilization involving fluorine atoms attached to $sp^2$ and $sp^3$ carbon is not significant in molecular crystal [Circled area in Fig 15(a) & (b)].

Figure 14: Variation of (a) electron density ($e/Å^3$) at BCP, (b) dissociation energy (D.E) (kcal/mol) with H⋯F bond path length (Å), (c) Laplacian ($∇^2 ρ$) at BCP and (d) $|V_b|/G_b$ with H⋯F bond path length (Å).
**Figure 15:** Comparison of variation of (a) dissociation energy (D.E) (kcal/mol) (b) electron density (e/Å³) at BCP and with H···F bond path length (Å) for C-H···F-C(sp²) [red curve] and C-H···F-C(sp³) [blue curve] [Total 153 data points (98 for red curve and 55 for blue curve)].

**Analysis of F···F bonding interactions**

There are numerous C-F···F-C interactions observed in the crystal packing of this series of compounds (Table S4 and S5). Hence, it was also of interest to do the topological characterization of F···F interactions. The nature and role of C-F···F-C interactions were recently studied both experimentally and theoretically by many researchers [75 -76]. The previous report by the QTAIM analysis of intramolecular C-F···F-C interactions on rigid isolated molecular system showed that these are closed shell interactions and can impart as much as 14 kcal/mol of local stabilization [77]. In the present work, QTAIM analysis of intermolecular C-F···F-C interactions has been performed and the result shows the exponential dependence of electron density at BCP (ρb), dissociation energy (D.E) and Laplacian (∇²ρ) of the electron density at BCP with the F···F bond path length (rᵢⱼ) (Fig. 16). Values of electron density and dissociation energy (local stabilization) was observed between ~0.060 > ρᵢⱼ(e/Å³) > ~0.010 and ~2.8 < D.E (kcal/mol) < ~0.5 for the ~2.80 > rᵢⱼ (Å) > 3.45. These values are slightly less or comparable with weak C-H···F-C interactions in the present work and observed to be similar to the previously observed values [67, 77, 78 - 80]. Furthermore, for the entire range of F···F bond path length, Laplacian (∇²ρ) > 1 and |V₀b|/G₀b < 1 were observed. Hence it can be concluded that the intermolecular F···F interactions in the present work are of closed shell in nature. Furthermore, the nature of C(sp³)/(sp²)-F···F-C(sp³)/(sp²) interactions from current and previous works along with reports
from experimental charge density analysis (Table 1) have been compared in Figure 17. The results shows the small differences in the in $\rho_b(\text{e/Å}^3)$ at BCP for different type of C-F···F-C interactions involving fluorine atoms attached to an $sp^2$ and $sp^3$ carbon atom. The shorter C-F···F-C interactions were observed to be associated with the C($sp^2$)-F bond in the molecule in the crystal. It is also of interest to notice variations in $\rho_b$, dissociation energy (D.E) and Laplacian ($\nabla^2 \rho$) of the electron density at the BCP for a given value of $r_{ij}$. Different value of electron density at BCP for C($sp^3$)/($sp^2$)-F···F-C($sp^3$)/($sp^2$) interactions for the nearly same $r_{ij}$ (Å) of F···F bond path (near to sum of van der Waals radii of the F-atom, 2.94 Å) in case of 3, 5, 6, 7, 8, 10 have been observed [Fig. 18]. This feature may be explained due to the cooperative interplay amongst the different possible intermolecular bond paths present in the motifs 3, 5, 6, 7 and 8 whereas in case of 10 (having the least value of $\rho_b$ among these), only one C($sp^3$)-F···F-C($sp^3$) is present.

Figure 16: Variation of (a) electron density (e/Å$^3$), (b) dissociation energy (D.E) (kcal/mol) with F···F bond path length (Å) [42 data points], (c) Laplacian ($\nabla^2 \rho$) at BCP and (d) $|V_b|/G_b$ with F···F bond path length (Å).
Figure 17: Comparison of the variation of the electron density (e/Å$^3$) at BCP and with F···F bond path length (Å) for C(sp$^3$)/sp$^2$···F-C(sp$^3$)/sp$^2$ interactions from current and previous works [Total 64 data points].

Table 1: Topological parameters from previous reports on C-F···F-C interactions by charge density analysis of high resolution X-ray data.

<table>
<thead>
<tr>
<th>Nature of Interactions</th>
<th>$R_{ij}$ (Å)</th>
<th>$\rho$ (e/Å$^3$)</th>
<th>$\nabla^2 \rho$ (e/Å$^5$)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(sp$^3$)-F···F-C(sp$^3$); Type I</td>
<td>2.8091</td>
<td>0.049</td>
<td>1.030</td>
<td>78</td>
</tr>
<tr>
<td>C(sp$^3$)-F···F-C(sp$^3$); Type I</td>
<td>2.8187</td>
<td>0.040</td>
<td>0.820</td>
<td>79</td>
</tr>
<tr>
<td>C(sp$^3$)-F···F-C(sp$^3$); Type II</td>
<td>2.8240</td>
<td>0.040</td>
<td>0.900</td>
<td>80</td>
</tr>
<tr>
<td>C(sp$^3$)-F···F-C(sp$^3$); Type II</td>
<td>2.9255</td>
<td>0.030</td>
<td>0.633</td>
<td>67</td>
</tr>
</tbody>
</table>
Figure 18: Showing first ten more stabilized motifs in Fig. 17, having \( C(sp^3)/(sp^2)-F \cdots F-C(sp^3)/(sp^2) \) interactions near or below to sum of van der Waal radii of two F-atoms, 2.94 Å.

Conclusion

Following the analysis of the 15 crystal structures (including one hydrate) from the 18 newly synthesized compounds along with the inputs from previously reported structures, the role of organic fluorine in the crystal packing have been analyzed in the presence of strong hydrogen bonds. Formation of many “reoccurring” structural motif by \( C_{sp^2}-F \) and \( CF_3 \) group have been identified and investigated in terms of their nature, energetics and topological properties which were quantified by the PIXEL method and QTAIM approach. It was observed that the highest stabilized molecular motifs primarily consist of \( C(sp^2)-H \cdots F-C(sp^2) \) hydrogen bond in preference to \( C(sp^2)-H \cdots F-C(sp^3) \) H bond in the crystal. Moreover, formation of hydrogen bond by \( C(sp^2)/(sp^3)-F \) group were observed to be present over the entire distance range between 2.2 to 2.7 Å (from the QTAIM approach), albeit the difference in energies of stabilization involving fluorine atoms attached to \( sp^2 \) and \( sp^3 \) carbon is not of significance in molecular crystals. Following the analysis of \( C(sp^2)/(sp^3)-F \cdots F-C(sp^2)/(sp^3) \) interactions from QTAIM approach, it was observed that these fulfill the criteria of these being of the closed shell type for the entire \( F \cdots F \) bond path length and provide local stabilization (indicates formation of bond) similar to the case of weak hydrogen bonds in crystals. For future study, it would be of interest to extend this
study to donor atoms in different hybridization environment with the F-C(sp²)/(sp³) group in different chemical environments. Furthermore, it is also of interest to investigate the effect of increasing fluorination on the molecule and the impact on the stabilization energies for the different supramolecular motifs involving organic fluorine present in the crystal.

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References:


40x23mm (300 x 300 DPI)